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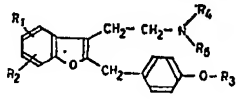
(54) NEW BENZOFURAN DERIVATIVES, THEIR PREPARATION AND USE

(71) We, CIBA-GEIGY A.G., a body corporate organised according to the laws of Switzerland, of CH 4002, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new benzofuran derivatives having valuable pharmacological properties, their addition salts with inorganic and organic acids, processes for the production of these new substances, as well as pharmaceutical preparations containing such substances and their use.

Surprisingly, it has been found that new benzofuran derivatives of the general formula I,



(I)

wherein

R_1 represents hydrogen, a halogen atom up to and including atomic number 35, an alkyl group or an alkoxy group, each with at most 2 carbon atoms, or the nitro group,

R_2 represents hydrogen, a halogen atom up to and including atomic number 35, an alkyl group or an alkoxy group, each with at most 2 carbon atoms,

R_3 represents an alkyl group, with at most 4 carbon atoms,

R_4 and R_5 each represent an alkyl group with at most 4 carbon atoms, or together they represent with the adjacent nitrogen atom the pyrrolidino, piperidino or morpholino group,

and their addition salts with inorganic and organic acids, possess valuable pharmacological properties, having in particular, analgesic as well as spasmolytic and antitussive activity, without CNS depressant activity. At the same time, they exhibit a relatively low toxicity and good compatibility and are therefore suitable as active substances of pharmaceutical preparations, which can be administered orally, rectally or parenterally, for the relief and removal of conditions of pain of varying origin, including those of a spasmodic nature, as well as tussive irritation. The analgesic effective-

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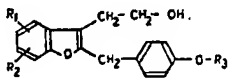
ness of the compounds of the general formula I and their acid addition salts:

1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl-3 - benzofuranyl] - ethyl] - pyrrolidine,
1 - [2 - [2 - (*p* - ethoxybenzyl) - 5,6-dimethyl - 3 - benzofuranyl] - ethyl] - pyrrolidine,
N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 6 - methyl - 3 - benzofuran] - ethylamine,
1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl-3 - benzofuranyl] - ethyl] - piperidine,
4 - [2 - [2 - (*p* - isopropoxybenzyl) - 5-methyl - 3 - benzofuranyl] - ethyl] - morpholine,
1 - [2 - [2 - (*p* - ethoxybenzyl) - 5-chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine,
N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuran] - ethylamine,
N,N - di - n - propyl - 2 - [2 - (*p*-ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine,
1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5-methyl - 3 - benzofuranyl] - ethyl] - piperidine,
1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5-methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine,
1 - [2 - [2 - (*p* - ethoxybenzyl) - 6-methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine,
1 - [2 - [2 - (*p* - ethoxybenzyl) - 6 - ethyl-3 - benzofuranyl] - ethyl] - pyrrolidine,
N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran] - ethylamine,

and their hydrochlorides, in the case of oral and intraperitoneal administration to mice, is shown, for example, in the Hot-Plate-Test according to A. D. Woolfe and G. McDonald, J. Pharmacol. Exptl. Therap. *80*, 300 (1944), whereby the lengthening of the reaction time, resulting from administration of the test substances, is determined in the case of mice placed on a plate at 56°. Moreover, the analgesic activity can be shown, e.g., by measurement of the lengthening of the reaction time, produced by the intraperitoneal or oral administration to mice of the test substances, in the case of irritation of the tail by heat radiation according to the experimental arrangement of H. Friebel and Cl. Reichle, Arch. exp. Path. and Pharmakol. *226*, 551 (1955). The antitussive activity of the compounds of the general formula I and their acid addition salts, e.g. the hydrochlorides of the N,N - dimethyl - 2 - [2 - (*p* - ethoxybenzyl) - 3-benzofuran] - ethylamine, the 4 - [2 - [2-(*p* - ethoxybenzyl) - 3 - benzofuranyl] - ethyl] - morpholine and the 4 - [2 - [2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - morpholine, is demonstrated, e.g., with the intravenous administration of the test substances to cats, according to the method of R. Domenjoz, Arch. exp. Path. and Pharmakol. *215*, 19—24 (1952). The musculotropic-spasmolytic activity of the new substances e.g. of the 1 - [2 - [2 - (*p*-ethoxybenzyl) - 3 - benzofuranyl] - ethyl] - pyrrolidine and its hydrochloride, is shown, for example, in tests of the isolated intestine of the guinea pig, whereby the dosages of the test substances are determined, which are equal in lytic effect to papaverine in counteracting the contraction produced by barium chloride.

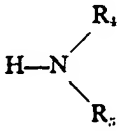
In the benzofuran derivatives of the general formula I and in the appertaining starting materials given below, R_1 is, as an alkyl or alkoxy group, the methyl, ethyl, methoxy or ethoxy group, and as a halogen atom, it is chlorine, fluorine or bromine. R_2 is hydrogen, one of the alkyl or alkoxy groups mentioned for R_1, especially the methyl or methoxy group, or one of the aforementioned halogen atoms. Examples of alkyl groups represented by R_3 are the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and sec-butyl groups. As alkyl groups, R_4 and R_5 are, e.g., methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl or sec. butyl groups.

The new benzofuran derivatives of the general formula I and their acid addition salts are produced by reacting a reactive ester of a compound of the general formula II,



(II)

wherein R_1, R_2 and R_3 have the meanings given under formula I, with a compound of the general formula III



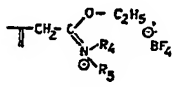
(III)

wherein R_4 and R_5 have the meanings given under formula I and, optionally, converting the obtained benzofuran derivative of the general formula I into an addition salt with an inorganic or organic acid.

Suitable as reactive esters of compounds of the general formula II are, e.g., sulphonic acid esters, such as the *p*-toluenesulphonic acid esters and the methanesulphonic acid esters, as well as hydrohalic acid esters such as, e.g., bromides and chlorides. As reaction medium and simultaneously as acid-binding agent, an

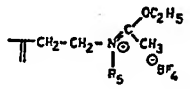
R_1, R_2, R_3 and R_5 have the meanings given under formula I, directly or after reaction with triethyloxonium fluoroborate to give the corresponding immonio-ethyl ester fluoroborate by means of a complex hydride and, optionally, converting the benzofuran derivative, embraced by the above defined general formula I, into an addition salt with an inorganic or organic acid.

The direct reduction of the compounds of the general formula VIII occurs, for example, by means of lithium aluminium hydride or diborane, which is either produced beforehand or is formed *in situ*, e.g. from potassium borohydride and boron trifluoride etherate, in an ethereal solvent such as tetrahydrofuran, diethyl ether, dibutyl ether or diethylene glycol dimethyl ether, at temperatures between ca. 20° and 100° or at the boiling temperature of the stated solvent. Instead of reducing the compounds of the general formula VIII directly, they may be firstly reacted with triethyloxonium fluoroborate in organic solvents inert to the latter such as, e.g., methylene chloride, to give the corresponding immonio-ethyl ester fluoroborates, e.g. those of the partial formulae VIIIa or VIIIb



VIIIa

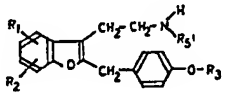
or



VIIIb

and these intermediate products reduced, e.g., either with an alkali metal borohydride, such as potassium borohydride, in a lower alkanol such as methanol, or with lithium aluminium hydride or diborane in an ethereal solvent. Amides of the general formula VIII which are 2 - (*p* - alkoxybenzyl) - 3 - benzofuranacetic acid amides can be produced, for example, from the alkyl esters of the corresponding carboxylic acids, which are mentioned above and given by the general formula VI, either in one stage by reaction with compounds of the general formula III, or in several stages by hydrolysis of the stated esters, transformation of the obtained carboxylic acids into reactive functional derivatives, such as chlorides, bromides or mixed anhydrides, and reaction of these derivatives with compounds of the general formula III. Further starting materials of the general formula VIII are, e.g., the derivatives wherein Z_1 represents a methylene group and Z_2 represents a carbonyl group, R_4' being an alkyl group independent of R_3, or forming an alkylene group in conjunction with R_5 as in, for example, 2 - (*p*-alkoxybenzyl) - 3 - [2 - (2 - oxo - 1-pyrrolidinyl) - alkyl] - benzofurans.

Such starting materials can be prepared, for example, by acylating secondary amines of the general formula IXa,



(IXa)

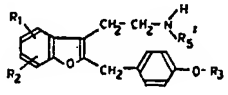
wherein

R_5'' represents an alkyl group with at most 4 carbon atoms, and

R_1, R_2 and R_3 have the meanings given under formula I,

with an alkanoic acid chloride or an alkanoic anhydride in the presence of pyridine, or by reacting reactive esters of compounds of the above defined general formula II with N-alkali metal derivatives of N - alkyl - carboxylic acid amides or, e.g., of 2-pyrrolidinone.

A third process for the production of the benzofuran derivatives of the general formula I and their acid addition salts consists in reacting a compound of the general formula IX,



(IX)

wherein

R_5' represents hydrogen or an alkyl group with at most 4 carbon atoms, and

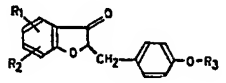
R_1, R_2 and R_3 have the meanings given under formula I,

with a lower oxoalkane containing maximally 4 carbon atoms under reducing conditions, or with a reactive ester of a lower alkanol containing maximally 4 carbon atoms in the presence of an acid-binding agent and, in each case, at least in the molar equivalent amount corresponding to the number of hydrogen atoms which are bound to the nitrogen atom to be replaced or, if R_5' is hydrogen, also with a reactive ester of 1,4-butanediol, 1,5-pentanediol or diethylene glycol in the presence of an acid-binding agent and, optionally, converting the obtained benzofuran derivative of the general formula I into an addition salt with an inorganic or organic acid.

For the reaction with an oxoalkane such as, e.g., formaldehyde or acetaldehyde under reducing conditions, hydrogen—at normal or moderately elevated pressures and tempera-

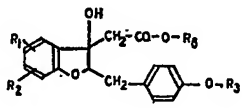
excess of the base of the general formula III to be reacted can be used, whereby the reaction is preferably performed between 60 and 120°C, i.e. at the boiling temperature of the base or, optionally, also below this temperature or above and, in the latter case, in a closed vessel. By using dimethylformamide as reaction medium and an excess of base as acid-binding agent, the reaction can be performed at room temperature to moderately elevated temperature. Furthermore, the reaction can be carried out, e.g., in ethanol, butanone and dioxane, preferably at their boiling point and using excess base of the general formula III or, e.g., tertiary organic bases or inorganic, acid-binding substances, e.g. carbonates such as potassium carbonate.

The benzofuran derivatives of the general formula II, from which the reactive esters can be produced in the usual manner, are for their part new substances. They are produced, e.g., starting with 3(2H)-benzofuranones, substituted according to the definitions for R_1 with the exception of the nitro group, and R_2. These are firstly condensed with *p*-alkoxybenzaldehydes and the obtained 2 - (*p*-alkoxybenzylidene) - derivatives are hydrogenated to give the corresponding 2 - (*p*-alkoxybenzyl) - 3(2H) - benzofuranones of the general formula IV,



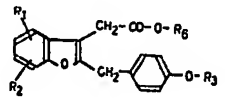
(IV)

wherein R_1, R_2 and R_3 have the meanings given under formula I. By reacting the compounds of the general formula IV with 2-bromoacetic acid alkyl esters and zinc in benzene, according to Reformatsky, there are obtained 2 - (*p* - alkoxybenzyl) - 3 - hydroxy-2,3 - dihydro - 3 - benzofuran - acetic acid alkyl esters, corresponding to the general formula V,



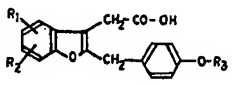
(V)

and from these are obtained by dehydration, e.g. by further reaction with dilute sulphuric acid immediately following the decomposition of the reaction mixture or by heating the isolated hydroxy ester alone or in the presence of a substance which splits off water, 2 - (*p*-alkoxybenzyl) - 3 - benzofuranacetic acid alkyl esters of the general formula VI



(VI)

which, in their turn, are optionally hydrolysed to the corresponding 2 - (*p* - alkoxybenzyl)-3 - benzofuran - acetic acids of the general formula VII,



(VII)

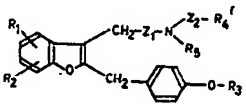
In the general formulae, V, VI and VII,

R_6 represents an alkyl group, with at most 4 carbon atoms, whilst

R_1, R_2 and R_3 have the meanings given under formula I.

The reduction of the esters of the general formula VI with complex hydrides such as, e.g., lithium aluminium hydride or diborane in ethereal solvents, yields 2 - [2 - (*p* - alkoxybenzyl) - 3 - benzofuran] - ethanols, which correspond to the general formula II. A further access to the above mentioned 2 - (*p*-alkoxybenzyl) - 3(2H) - benzofuranones of the general formula IV consists in the ring-closing condensation of (*o* - alkoxycarbonylphenoxy)-acetic acid alkyl esters, optionally substituted according to the definitions of R_1 and R_2, by means of sodium to give sodium compounds of 3(2H) - oxo - 2 - benzofurancarboxylic acid alkyl esters, followed directly by reaction with *p*-alkoxybenzyl bromides or chlorides and final decarbalkoxylation by means of methanolic potassium hydroxide solution at boiling temperature.

According to a second process, compounds of the general formula I and their acid addition salts are produced by reducing a compound of the general formula VIII,



(VIII)

wherein one of the symbols Z_1 and Z_2 represents a methylene group, and the other a carbonyl group, and

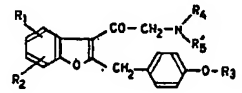
R_4' represents an alkyl group with at most 3 carbon atoms or together with R_5, Z_2 and the adjacent nitrogen atom, depending on the meaning of Z_2, an optionally carbonyl-substituted pyrrolidino, piperidino or morpholino group, and

tures—is allowed to act, e.g., on a solution of the starting material of the general formula IX wherein R_1 does not represent the nitro group, and the oxoalkane in a suitable organic solvent such as, e.g., ethanol or dioxane, in the presence of a hydrogenation catalyst such as, e.g., Raney nickel, platinum oxide or palladium-charcoal. If a compound of the general formula I, in which a methyl group or groups is/are to be present as R_1 or R_4 and R_5 is to be produced by reaction with excess formaldehyde, formic acid can also be used as a reducing reaction medium, at moderately elevated temperature to boiling temperature.

As reactive esters of alkanols or reactive diesters of the 1,4-butanediol, 1,5-pentanediol or diethylene glycol, halides or dihalides, especially bromides or dibromides, are preferably used, as well as iodides or chlorides or diiodides or dichlorides. The reactions are performed hot, e.g. at the boiling temperature of the solvent used, e.g. in organic solvents such as, e.g., acetonitrile or methanol, or without a solvent in the presence of acid-binding agents such as, e.g., sodium or potassium carbonate, or in an excess of the compound to be reacted of the general formula IX.

Starting materials of the general formula IX having a hydrogen atom as R_5' are produced, e.g., starting with 3(2H)-benzofuranones, optionally substituted corresponding to the definition for R_1 and R_2. From the latter are firstly produced, by condensation with bromoacetic acid alkyl esters in the presence of zinc in benzene and subsequent dehydration, the corresponding 3-benzofuranacetic acid alkyl esters, the reduction of which with lithium aluminium hydride or diborane, e.g. in tetrahydrofuran, yields the corresponding 2 - [3 - benzofuran) - ethanols. These alcohols are converted into reactive esters, e.g. *p*-toluenesulphonic acid esters or chlorides or bromides, and the latter converted with ammonia into corresponding 2 - [3 - benzofuran] - ethylamines. These amines are reacted with *p* - alkoxy - benzoyl chlorides in pyridine to give N - (*p* - alkoxybenzoyl) derivatives, from which are obtained with the action of condensation agents, e.g. phosphorus pentoxide and phosphorus oxychloride in boiling toluene, with ring closure between the amide group and the 2-position of the benzofuran, 1 - (*p* - alkoxyphenyl) - 3,4 - dihydrobenzofuro - [2,3 - c] - pyridines, which are optionally substituted in the benzene nucleus corresponding to the definitions of R_1 and R_2. By reductive splitting of these tricyclic compounds by means of hydrazine, e.g. in the presence of sodium hydroxide in diethylene glycol at temperatures of about 200°, compounds of the general formula IX are finally obtained, i.e. 2 - [2 - *p* - alkoxybenzyl) - 3-benzofuran] - ethylamines or derivatives thereof, substituted in the benzene nucleus corresponding to the definitions of R_1 and R_2. A further possibility of production for the stated amines and also for such amines of the general formula IX, wherein R_5' represents a alkyl group, consists of the reaction of the above stated esters of the general formula VI with ammonia or alkylamines or also by the acylation of primary amines of the general formula IX, wherein R_5' represents hydrogen and R_1, R_2 and R_3 have the meanings given in formula I, with an alkanoic acid chloride or anhydride to the corresponding secondary amides, and subsequent reduction of the amides thus obtained with lithium aluminium hydride or diborane analogously to the second mentioned process for the production of the compounds of the general formula I.

According to a fourth process, benzofuran derivatives of the general formula I and their acid addition salts are produced by reducing a compound of the general formula X,



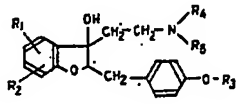
(X)

wherein
R_1, R_2, R_3, R_4 and R_5 have the meanings given under formula I, by means of a complex hydride in the presence of a Lewis acid in an ethereal solvent and, optionally, converting the obtained benzofuran derivative, embraced by the general formula I, into an addition salt with an inorganic or organic acid. For example, diborane in tetrahydrofuran, dibutyl ether or diethylene glycol dimethyl ether is allowed to act, at temperatures between 50° and 100° or at the boiling temperature of the solvent, on a compound of the general formula X in the presence of boron trifluoride etherate, or to a solution of the starting material in the same reaction medium is slowly added, in the presence of an excess of boron trifluoride etherate, the amount of lithium aluminium hydride or potassium borohydride which is necessary for the reduction.

The starting materials of the general formula X are produced, for example, starting with 2 - (*p* - alkoxybenzyl) - benzofurans, which can be substituted corresponding to the definitions of R_1 and R_2, by condensation with acetyl chloride according to the Friedel-Crafts reaction, e.g. with the aid of tin tetrachloride in carbon disulphide, subsequent bromination of the obtained 3-acetyl compounds and reaction of the latter with compounds of the above stated general formula III.

According to a fifth process, the benzofuran derivatives of the general formula I

and their acid addition salts are produced by subjecting a compound of the general formula XI,



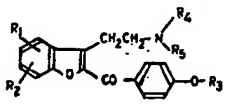
(XI)

wherein R_1, R_2, R_3, R_4 and R_5 have the meanings given under formula I, to conditions under which water is split off and, optionally, converting the obtained benzofuran derivative of the general formula I into an addition salt with an inorganic or organic acid. By conditions under which water is split off is meant, e.g., either the treatment of the compounds of the general formula X with agents splitting off water, e.g. with strong acids such as *p*-toluenesulphonic acid, hydrochloric acid or sulphuric acid, in inert organic solvents at room temperature or at moderately elevated temperatures, e.g. around 80—120°, or heating of the compounds in the absence of agents splitting off water, but optionally in the presence of higher-boiling solvents, to temperatures between ca. 120 and 200°.

The production of the starting materials of the general formula XI can be carried out starting with the above stated Reformatsky reaction products of the general formula V. Instead of dehydrating these hydroxy esters firstly to compounds of the general formula VI, they are reduced directly to the corresponding 2 - [2 - (*p* - alkoxybenzyl) - 3-hydroxy - 2,3 - dihydro - 3 - benzofuran]-ethanols. These are converted at low temperatures with *p*-toluenesulphochloride in pyridine into their *p*-toluenesulphonic acid esters. The starting materials of the general formula XI are obtained by reaction of the *p*-toluenesulphonic acid esters with compounds of the general formula III, analogously to the first mentioned process for the production of the benzofuran derivatives of the general formula I.

By the reaction of the *p*-toluenesulphonic acid 2 - [2 - (*p* - alkoxybenzyl) - 2,3 - dihydro - 3 - hydroxy - 3 - benzofuranyl)-ethyl ester with amines of the general formula III, the thermal splitting off of water can occur from the first formed compounds of general formula XI, wherein R_1 does not represent a halogen atom, to give directly, compounds of the general formula I.

According to a sixth process, the benzofuran derivatives of the general formula I and their acid addition salts are produced by reducing a compound of the general formula XII



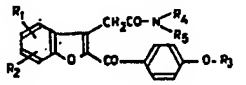
(XII)

wherein
R_1, R_2, R_3, R_4 and R_5 have the meanings given under formula I by means of a complex hydride or hydrazine hydrate in the presence of an alkali metal hydroxide, and optionally converting the benzofuran derivative of the general formula I thus obtained into an addition salt thereof with an inorganic or organic acid.

For example, a compound of the general formula XII is allowed to react with diborane in tetrahydrofuran at room temperature or hydrazine hydrate in diethyleneglycol at a temperature of about 200°.

The starting material of the general formula XII is obtained, for example, starting from an alkanoic acid 2 - (3 - benzofuranyl)ethyl ester, which can be substituted according to the definitions given for R_1 and R_2, by reaction with a *p*-alkoxybenzoyl chloride, e.g. using tin tetrachloride or titanium tetrachloride in carbon disulphide, saponification of the corresponding 2 - [2 - (*p* - alkoxybenzoyl) - 3 - benzofuran] - ethanols and subsequent reaction of the reactive esters themselves with amines of the above mentioned general formula III.

According to a seventh process, benzofuran derivatives of the general formula I and their acid addition salts can be produced by reducing a compound of the general formula XIII



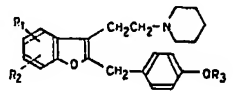
wherein
R_1, R_2, R_3, R_4 and R_5 have the meanings given under formula I by means of a complex hydride and optionally converting the benzofuran derivative of the general formula I thus obtained into an addition salt thereof, with an inorganic or organic acid.

For example, a compound of the general formula XIII is allowed to react with a solution of diborane in, e.g., tetrahydrofuran at room temperature or a slightly raised temperature.

The starting material of the general formula XIII is prepared, for example, starting from 3-benzofuranacetic acid alkyl esters, which can be substituted according to the definitions given for R_1 and R_2 by reaction

with a *p*-alkoxybenzoyl chloride, e.g. using tin tetrachloride or titanium tetrachloride in carbon disulphide, to give 2 - (*p* - alkoxybenzoyl) - 3 - benzofuran - acetic acid alkyl esters, and reaction of the same with an amine of the general formula III, optionally in the presence of a sufficient amount of methanol for the esterification with a basic catalyst of the 2 - (*p* - alkoxybenzoyl) - 3 - benzofuran-acetic acid ethyl ester to the corresponding methyl ester at the boiling point of the amine or in a pressure vessel at a temperature of 80—130°.

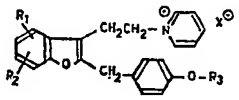
According to an eighth process benzofuran derivatives of the general formula Ia,



(Ia)

wherein

R_1, R_2 and R_3 have the meanings given under formula I, except that R_1 may not represent a nitro group, are prepared by reducing a compound of the general formula XIV



(XIV)

in which

R_1, R_2 and R_3 have the meanings given under formula I, except that R_1 may not represent a nitro group, and

$X^{\ominus}$ represents a monovalent anion or the normal equivalent of a polyvalent anion, by means of catalytically activated hydrogen.

The hydrogenation can be carried out, for example, in the presence of a platinum catalyst until the required amount of hydrogen has been taken up.

The pyridinium compound of the general formula XIV required as starting material is prepared, for example, by the reaction of a reactive ester of a compound of the general formula II with pyridine at a slightly raised temperature. As the reactive ester can be, e.g., the bromide or the *p*-toluene-sulphonic acid ester.

Optionally, the benzofuran derivatives of the general formula I, obtained according to the invention, are subsequently converted in the usual manner into their addition salts with inorganic and organic acids. For example, the acid desired as salt component, or a solution thereof, is added to a solution of a compound of the general formula I in an organic solvent such as acetone, dioxane, methanol or ethanol or diethyl ether and the salt separated which precipitates directly or after addition of a second organic liquid such as, e.g., diethyl ether, acetone, water or water-miscible solvents, such as acetone or dioxane.

Optionally, for use as active substances for medicaments, it is possible to use instead of free bases, and preferably in solutions, pharmaceutically acceptable acid addition salts, i.e. salts with such acids, the anions of which, in the case of the dosages in question, have either no inherent pharmacological action or a desired one. Moreover, it is of advantage if the salts to be used as active substances crystallise well and are not, or are only slightly, hygroscopic. For salt formation with compounds of the general formula I, it is possible to use, e.g., hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanedisulphonic acid, β-hydroxyethanesulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, succinic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid, embonic acid or 1,5-naphthalene-disulphonic acid.

The new benzofuran derivatives of the general formula I and their pharmaceutically acceptable acid addition salts are administered orally, rectally or parenterally. For the treatment of conditions of pain in the case of mammals, daily dosages of 0.1—5 mg/kg (preferably 0.1—1.0 mg/kg) are administered parenterally and daily dosages of 5—100 mg/kg (preferably 5—20 mg/kg) orally or rectally. For the treatment of tussive irritation, the daily dosage, orally or parenterally, for warm-blooded animals is 0.25—2.5 mg/kg. Dosage units suitable for oral or rectal administration, such as dragées, capsules, tablets or suppositories, preferably contain 10—100 mg, and ampoules preferably contain 5—25 mg of a benzofuran derivative of the general formula I, or of a pharmaceutically acceptable salt thereof.

In a further aspect therefore, the present invention provides a pharmaceutical composition comprising a benzofuran derivative of the general formula I defined above, or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier therefor.

Dosage units for oral administration preferably contain as active substance between 5% and 90% by weight of a benzofuran derivative of the general formula I or a pharmaceutically acceptable salt thereof. They are produced by combining the active substance, e.g., with solid pulverulent carriers such as lactose, saccharose, sorbitol or mannitol; starches such as potato starch, maize starch or amylopectin, laminaria powder or citrus

pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants, such as magnesium or calcium stearate or polyethylene glycols, to form tablets or dragée cores. The latter are coated, e.g., with concentrated sugar solutions which can also contain, e.g., gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in readily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g., to distinguish between varying dosages of active substance. Also suitable as oral dosage units are hard gelatine capsules as well as soft closed capsules made from gelatine and a softener, such as glycerin. The former preferably contain the active substance as a granulate in admixture with lubricants such as talcum or magneseum stearate and, optionally, stabilisers such as sodium metabisulphite or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids, such as liquid polyethylene glycols, whereby stabilisers can likewise be added.

Also suitable for the treatment of coughing are, e.g., sucking tablets as well as oral preparations not administered in a single dosage such as, e.g., cough syrup and cough drops, which are prepared with the usual auxiliary agents.

Suitable dosage units for rectal administration are, e.g. suppositories consisting of a combination of a benzofuran derivative of the general formula I, or of a suitable salt thereof, with a neutral fatty base and, in addition, gelatine rectal capsules containing a combination of the active substance with polyethylene glycols.

Ampoules for parenteral, especially intramuscular and also intravenous administration, preferably contain a water-soluble salt of a benzofuran derivative of the general formula I as active substance in a concentration of preferably 0.5—5% by weight, optionally together with suitable stabilising agents and buffer substances in aqueous solution.

The following prescriptions further illustrate the production of preparations according to the invention:

a) 10 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl]-ethyl] - pyrrolidine hydrochloride, 30 g of lactose and 5 g of highly dispersed silicic acid are mixed. The mixture is moistened with a solution of 5 g of gelatine and 7.5 g of glycerin in distilled water, and is granulated through a sieve. The granulate is dried, sieved and carefully mixed together with 3.5 g of potato starch, 3.5 g of talcum and 0.5 g of magnesium stearate. The mixture is pressed into 1000 tablets each weighing 65 mg and each containing 10 mg of active substance.

b) 1000 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl]-ethyl] - piperidine hydrochloride are mixed together with 550 g of lactose and 292 g of potato starch. The mixture is moistened with an alcoholic solution of 8 g of gelatine and granulated through a sieve. After drying, 60 g of potato starch, 60 g of talcum, 10 g of magnesium stearate and 20 g of highly dispersed silicon dioxide are mixed in. The mixture is then pressed into 10,000 tablets each weighing 200 mg and each containing 100 mg of active substance, whereby the tablets can optionally be provided with grooves for more accurate adjustment of the dosage amount.

c) 10 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5,6 - dimethyl - 3 - benzofuranyl]-ethyl] - pyrrolidine hydrochloride, 15 g of lactose and 20 g of starch are mixed together. The mixture is moistened with a solution of 5 g of gelatine and 7.5 g of glycerine in distilled water and granulated through a sieve. The granulate is dried, sieved and carefully mixed with 3.5 g of talcum and 0.5 g of magnesium stearate. The mixture is pressed into 1000 dragée cores. Theses are subsequently coated with a concentrated syrup made from 26.66 g of crystallised saccharose, 17.5 g of talcum, 1 g of shellac, 3.75 g of gum arabic, 1 g of highly dispersed silicic acid and 0.090 g of dyestuff, and dried. The obtained dragées each weigh 115 mg and each contain 10 mg of active substance.

d) A granulate is produced from 500 g of N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuran]-ethylamine hydrochloride, 175.90 g of lactose and an alcoholic solution of 10 g of stearic acid. After drying, the granulate is mixed with 56.60 g of highly dispersed silicon dioxide, 165 g of talcum, 20 g of potato starch and 2.50 g of magnesium stearate and the mixture pressed into 10,000 dragée cores. These are subsequently coated with a concentrated syrup made from 502.28 g of crystallised saccharose, 6 g of shellac, 10 g of gum arabic, 0.22 g of dyestuff and 1.5 g of titanium dioxide, and dried. The obtained dragées each weigh 145 mg and each contain 50 mg of active substance.

e) To produce 1000 capsules each containing 25 mg of active substance, 25 g of 1-[2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro-3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride are mixed with 248 g of lactose. The mixture is evenly moistened with an aqueous solution of 2 g of gelatine and granulated through a suitable sieve (e.g. sieve III according to Ph. Helv. V). The granulate is mixed together with 10 g of dried maize starch and 15 g of talcum and the mixture is uniformly filled into 1000 hard gelatine capsules, size 1.

f) A suppository mixture is prepared from 5 g of 4 - [2 - [2 - (*p* - isopropoxybenzyl)-5 - methyl - 3 - benzofuranyl] - ethyl]-morpholine hydrochloride and 163.5 g of adeps

solids and from the mixture are poured 100 suppositories each containing 50 mg of active substance.

g) 1 g of 1 - [2 - [2 - (*p* - ethoxybenzyl)-5 - methyl - 3 - benzofuranyl] - ethyl]-pyrrolidine hydrochloride and 0.10 g of ascorbic acid are dissolved in distilled water and diluted to 100 ml. The obtained solution is used to fill ampoules, each with a content, e.g., of 1 ml, corresponding to a content of 10 mg of active substance. The filled ampoules are sterilised by heating in the usual manner.

h) 1 g of 1 - [2 - [2 - (*p* - ethoxybenzyl)-5 - methyl - 3 - benzofuranyl] - ethyl]-pyrrolidine hydrochloride and 4.4 g of glycerin are dissolved in distilled water to give 200 ml and the solution is filled into 100 ampoules each of 2 ml and each containing 10 mg of active substance.

i) To produce a syrup having an active substance content of 0.5% (weight per volume), 0.50 g of N,N - dimethyl - 2 - [2 - (*p*-ethoxybenzyl) - 3 - benzofuran] - ethylamine hydrochloride and 0.1 g of odorous substance are dissolved in 65 ml of 96% ethanol. On the other hand, 3 g of sugar, 0.6 g of saccharin are dissolved in 10 ml of hot distilled water, whereby 5 g of glycerin are added and the obtained solution is combined with the aforementioned active substance solution and the quantity made up to 100 ml with ethanol.

The following examples illustrate the production of the new benzofuran derivatives of the general formula I but they in no way limit the scope of the invention. The temperatures throughout this specification are given in degrees Centigrade.

EXAMPLE 1

a) 40 g of 5 - methyl - 3(2H) - benzofuranone [cp. K. Feist and E. Siebenlist, Arch. Pharm. *265*, 196 (1927)] are dissolved in 35 ml of hot absolute ethanol. To this solution are added 40.5 g of *p*-ethoxybenzaldehyde and 2 ml of concentrated hydrochloric acid and the solution is then refluxed for half an hour at boiling temperature. The acid solution produces a deep red colouration of the solution and an exothermic reaction. After a short time, the benzylidene compound commences to precipitate. After cooling, the reaction mixture is allowed to stand for ca. 15 hours at 0°, whereupon the reaction product is filtered with suction and washed with a little ethanol. 54 g (71.5% of theoretical amount) of 2 - (*p* - ethoxybenzylidene) - 5-methyl - 3(2H) - benzofuranone are obtained as yellow needles, M.P. 140—142° after recrystallisation from ethanol.

b) 38 g of 2 - (*p* - ethoxybenzylidene)-5 - methyl - 3(2H) - benzofuranone (in 700 ml of dioxane) are added to 7 g of prehydrogenated catalyst (5% palladium on barium carbonate) and hydrogenated at room temperature under normal pressure. After 5 hours, the hydrogen absorption is over 90% of the theoretical value and the initially yellow solution is practically decolourised. As soon as no further hydrogen absorption occurs, the catalyst is removed by filtration and the filtrate concentrated by evaporation *in vacuo*. By crystallisation of the residue from ether/petroleum ether are obtained 30 g of 2 - (*p*-ethoxybenzyl) - 5 - methyl - 3(2H) - benzofuranone as yellowish crystals, M.P. 74.5—75°, yield 75% of theoretical amount.

c) 17.0 g of 2 - (*p* - ethoxybenzyl) - 5-methyl - 3(2H) - benzofuranone and 43.0 g of bromoacetic acid methyl ester are dissolved in 300 ml of absolute benzene and slowly added dropwise, whilst vigorously stirring, to a mixture of 22 g of zinc wool, 0.1 g of mercury(II) chloride and 100 ml of boiling benzene. Practically the whole of the zinc has dissolved after 3 hours. The reaction mixture is then refluxed at boiling temperature for a further 4 hours. It is then cooled to room temperature and decomposed with 200 ml of 2N sulphuric acid. To split off water from the stereoisomeric 2 - (*p* - ethoxybenzyl) - 3-hydroxy - 3 - benzofuranacetic acid methyl esters, the two-phase mixture is stirred until a specimen of the benzene phase exhibits only a main spot (Rf=ca. 0.8) in the thin-layer chromatogram (carrier = aluminium oxide neutral "Merck", solvent benzene/ether (1:1 v/v), colouration by heating to 100° after spraying with 10% sulphuric acid in ethanol). The benzene layer is then taken off, washed neutral, dried over sodium sulphate and filtered through a chromatography column charged with 500 g of neutral aluminium oxide, Woelm activity degree III. Eluting of the partially absorbed reaction product with benzene and concentrating by evaporation of the extract combined with the filtrate yields 15.9 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3-benzofuranacetic acid methyl ester as a yellowish oil (yield 78% of theoretical value). The ester crystallises from petroleum ether as colourless needles, M.P. 70—71°. A sample of the ester, refluxed with 1N potassium hydroxide solution in aqueous ethanol for 2 hours yields, after evaporating off the ethanol, acidifying with 2N sulphuric acid, extracting with ether and crystallising from ether/petroleum ether, the corresponding acid, M.P. 174—175°.

c') 2.7 grams of 2 - (*p* - ethoxybenzyl - 5-methyl - 3(2H) - benzofuranone are reacted analogously to Example 1c) with 6.6 grams of bromoacetic acid methyl ester and 3.3 grams of zinc wool. 20 ml of 2N-sulphuric acid are then added and the mixture is stirred for about 2 minutes. The benzene phase is washed neutral, dried over sodium sulphate and evaporated. The residual 3.3 g of oily raw product are chromatographed on 130 g of neutral aluminium oxide, Woelm Activity Stage III. Fractions of 100 ml each are taken according to the table shown below:

Fraction Number	Solvent (V/V)	Residue after Evaporation (g)
1	Benzene	1.63
2	Benzene	0.58
3	Benzene	0.05
4	Benzene	0.16
5	Benzene/ether (9:1)	0.16
6	Benzene/ether (5:1)	0.28
7	Benzene/ether (5:1)	0.22
8	Benzene/ether (5:1)	0.05

The combined fractions 1 and 2 give from petroleum ether 2.1 g of 2 - (*p* - ethoxybenzyl) 5 - methyl - 3 - benzofuran - acetic acid methyl ester, M.P. 70—71°. From the combined fractions 7 and 8 is obtained, after crystallisation from ether/petroleum ether, 0.18 g of racemic 2 - (*p* - ethoxybenzyl) - 5-methyl - 2,3 - dihydro - 3 - hydroxy - 3-benzofuran - acetic acid methyl ester, M.P. 81—82° designated here as "racemate B". The corresponding "racemate A" remains in the fractions 5 and 6 as a colourless oil. (IR in CH_2Cl_2: 3540 cm^{-1}OH, 1730 cm^{-1}CO.)

d) 3.6 g of 2 - (*p* - ethoxybenzyl) - 5-methyl - 3 - benzofuran - acetic acid methyl ester, dissolved in 10 ml of absolute tetrahydrofuran, are added dropwise, while stirring, to a suspension of 1.5 g of lithium aluminium hydride in 30 ml of absolute tetrahydrofuran and the mixture is refluxed for 3 hours. The mixture is then cooled with ice and decomposed with dilute hydrochloric acid. After the addition of 10 ml of a semi-saturated solution of potassium sodium tartrate and neutralisation with concentrated aqueous ammonia solution, the tetrahydrofuran is evaporated off *in vacuo* and the mixture, diluted with water, is repeatedly extracted with ether. The ether extracts, washed neutral and dried over sodium sulphate, are filtered through 20 g of neutral aluminium oxide of Woelm activity stage III and eluted with ether. Filtrate and extracts yield, after concentration by evaporation, 3.0 g (91% of theoretical value) of 2 - [2 - (*p* - ethoxybenzyl) - 5-methyl - 3 - benzofuran]ethanol as colourless oil.

e) 3.0 g of the alchool, obtained according to d), are dissolved in 10 ml of absolute pyridine and the solution is cooled to −10°. To this are added 5.0 g of p-toluenesulphochloride in portions in such a manner that the temperature does not exceed −5°. The mixture is allowed to stand for 15 hours at 0°, whereupon it is poured into ice water and the precipitated oil separated and triturated. Crystallisation occurs after some time. Recrystallisation from ether/petroleum ether yields 3.2 g of *p*-toluenesulphonic acid 2 - [2 - (*p*-ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl]-ethyl ester, M.P. 78—79° (yield 71%).

f) 2.3 g of *p*-toluenesulphonic acid 2 - [2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester and 10 ml of pyrrolidine are refluxed for 4 hours. The reaction solution is then completely concentrated by evaporation *in vacuo*, 20 ml of benzene are added and again it is completely concentrated by evaporation. The residue is taken up in water and ether. The ethereal phase is repeatedly washed with water and then extracted three times using 5 ml of 1N hydrochloric acid each time. The acid extracts are adjusted with concentrated ammonia to pH 9 and the hereby precipitated oily base is extracted by being shaken with ether. The ethereal extract, washed with water, is dried over sodium sulphate and concentrated by evaporation *in vacuo*. The obtained crude 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl-3 - benzofuranyl] - ethyl] - pyrrolidine is dissolved in ether and to the solution is added a slight excess of ethereal hydrochloric acid. The precipitated hydrochloride crystallises upon triturating. After recrystallisation from acetone/ether are obtained 1.6 g of colourless crystals of the 1 - [2 - [2 - (*p* - ethoxybenzyl)-5 - methyl - 3 - benzofuranyl] - ethyl]-pyrrolidine hydrochloride, M.P. 167—169°, yield 80% of theoretical value.

EXAMPLE 2

a) 2.3 g of *p*-toluenesulphonic acid 2 - [2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester [cp. Example 1a)—e)] are refluxed for 24 hours, while stirring, with 0.6 ml of piperidine and 2.8 g of potassium carbonate in 20 ml of butanone. The inorganic salts are separated by filtration and the filtrate concentrated by evaporation *in vacuo*. The obtained crude 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine is dissolved in ether and a slight excess of ethereal hydrogen chloride is added. The precipitated hydrochloride is separated and recrystallised from acetone. By this means are obtained 1.5 g of 1 - [2 - [2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 192—193°. Yield 73% of theoretical value.

b) The hydrogen oxalate melts at 214—215° with decomposition (from methanol/acetone).

c) In an analogous manner 0.60 g of crude 5 - methyl - 2 - (*p* - ethoxybenzyl) - 3-benzofuranyl ethyl bromide are reacted with 0.15 ml of piperidine and 1.0 g of potassium carbonate in 5 ml of butanone. 1 - [2 - [2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 192—193°, is obtained after recrystallisation from acetone 0.44 g (yield 66%.) Simi lisation from acetone 0.44 g (yield 66%.) Similarly, with 0.15 ml of pyrrolidine, 1 - [2-[2 - (*p* - ethoxybenzyl) - 5 - methyl - 3-benzofuranyl] - ethyl] - pyrrolidine hydrochloride is obtained, M.P. 167—169° (yield 70% of theory).

The required starting material, 5 - methyl-2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl-ethyl bromide, is prepared as follows:

0.56 g of 2 - [5 - methyl - 2 - (*p* - ethoxybenzyl) - 3 - benzofuran] - ethanol are dissolved in 1.0 ml of absolute pyridine, the solution cooled to −15° and 0.15 ml of thionyl bromide added. At this point a formation of precipitate and a rise of temperature to −2° is observed. After keeping this solution at 0° for 48 hours, water is added and the precipitated oil taken up in ether and washed with N-hydrochloric acid and water. The ether phase is dried over sodium sulphate and evaporated. There remains 0.6 g of crude 2 - [5 - methyl - 2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl - ethyl bromide, a yellow oil.

EXAMPLE 3

2.3 g of *p*-toluenesulphonic acid 2 - [2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester [cp. example 1a)—e)] are refluxed with 10 ml of diethylamine for 48 hours. The reaction solution is then completely concentrated by evaporation *in vacuo*, 20 ml of benzene are added and the solution is again completely concentrated by evaporation. The residue is taken up in water and ether. The ethereal phase is repeatedly washed with water and then extracted three times using 5 ml of 1N hydrochloric acid each time. The acid extracts are adjusted to pH 9 with concentrated ammonia and the thereby precipitated (oily) base is extracted by shaking with ether. The ethereal extract, washed with water, is dried over sodium sulphate and concentrated by evaporation *in vacuo*. The crude, residual, N,N - diethyl - 2-[2 - (*p* - ethoxybenzyl) - 5 - methyl - 3-benzofuran] - ethylamine is dissolved in ether and a slight excess of ethereal hydrochloric acid is added. The precipitated hydrochloride is recrystallised from acetone/ether, whereby 1.5 g of N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran]-ethylamine hydrochloride are obtained as colourless crystals, M.P. 139—140°. Yield 72% of theoretical value).

EXAMPLE 4

2.3 g of *p*-toluenesulphonic acid 2 - [2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester [cp. example 1a)—e)] are refluxed with 10 ml of morpholine for 4 hours. The reaction solution is then completely concentrated by evaporation *in vacuo*, 20 ml of benzene are added and the solution is again completely concentrated by evaporation. The residue is taken up in water and ether. The ethereal phase is repeatedly washed with water and then extracted three times using 5 ml of 1N hydrochloric acid each time. The acid extracts are adjusted to pH 9 with concentrated ammonia and the thereby precipitated (oily) base is extracted with ether. The ethereal extract, washed with water, is dried over sodium sulphate and concentrated by evaporation *in vacuo*. The crude, residual, 4-[2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl-3 - benzofuranyl] - ethyl] - morpholine is dissolved in ether and to the solution is added a slight excess of ethereal hydrochloric acid. The precipitated hydrochloride crystallises upon triturating. After recrystallisation from acetone/ether there are obtained 1.9 g of colourless crystals of the 4 - [2 - [2 - (*p*-ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - morpholine hydrochloride, M.P. 172—174°. Yield 93% of theoretical value.

EXAMPLE 5

a) 2.3 g of *p*-toluenesulphonic acid 2-[2 - (*p* - ethoxybenzyl) - 5 - methyl - 3-benzofuranyl] - ethyl ester [cp. example 1a)—e)] are dissolved in 30 ml of a saturated solution of dimethylamine in dimethylformamide and allowed to stand for 24 hours at room temperature. The reaction solution is then concentrated by evaporation *in vacuo* and the residue taken up with water and ether.

The ethereal phase is washed with water, dried over sodium sulphate and concentrated by evaporation *in vacuo*. The crude N,N-dimethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5-methyl - 3 - benzofuran] - ethylamine which remains is dissolved in ether and a slight excess of ethereal hydrochloric acid is added. The precipitated hydrochloride is separated and recrystallised from acetone/ether, whereby 1.7 g of N,N - dimethyl - 2 - [2 - (*p*-ethoxybenzyl) - 5 - methyl - 3 - benzofuran]-ethylamine hydrochloride, M.P. 156—158°, are obtained. Yield 91% of theoretical value.

b) In an analogous manner 2.3 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl]-ethyl ester are reacted with 10 ml of di-n-propylamine to give N - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl]-ethyl] - di - n - propylamine, the hydrochloride of which melts, after recrystallisation from acetone/ether, at 107—108° (yield 1.46 g, 64% of Theory).

Similarly, 2.3 g of *p*-toluenesulphonic acid-2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl-3 - benzofuranyl] - ethyl ester are reacted with 10 ml of di-n-butylamine to give N-[2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl-3 - benzofuranyl] - ethyl] - di - n - butylamine, the hydrochloride of which, after recrystallisation from acetone/ether, melts at 106—107° (yield 1.0 g, 45% of Theory).

EXAMPLE 6

a) 40.0 g of [4 - methoxy - 2 - (methoxycarbonyl) - phenoxy] - acetic acid methyl ester [M.P. 77—79° from ether/petroleum ether, cp. K. v. Auwers, Ann. *393*, 352 (1912)] or 44.5 g of [4 - methoxy - 2 - (ethoxycarbonyl)-phenoxy] - acetic acid ethyl ester (B.P. 157—161°/0.7 Torr) are added in portions at 80°, while stirring, to 3.64 g of finely dispersed sodium in 100 ml of toluene. A thick slurry is formed with the dissolving of the sodium. As soon as all the sodium is dissolved (after ca. 3 hours), 34.0 g of *p*-ethoxybenzyl bromide are added, while stirring, to the obtained sodium compound of the 5 - methoxy - 3(2H)-oxo - 2 - benzofurancarboxylic acid methyl ester (or ethyl ester). The reaction mixture is subsequently refluxed while stirring for 20 hours. The mixture is then cooled and water is added. The organic phase is separated, washed neutral, dried over sodium sulphate and concentrated by evaporation. Ca. 24.0 g of substance, B.P. 116—120°/10 Torr, are distilled off from the residue under 10 Torr. The distillation residue of crude 2 - (*p*-ethoxybenzyl) - 5 - methoxy - 3(2H) - oxo-2 - benzofurancarboxylic acid methyl ester (or ethyl ester) is refluxed for one hour, to split off the carbalkoxy group, with 50 ml of 10% methanolic potassium hydroxide solution. The methanol is then evaporated off *in vacuo* and the residue taken up with water and ether. The ether phase is washed neutral, dried over sodium sulphate and filtered through 100 g of neutral aluminium oxide of Woelm activity stage III. The extract, obtained by after-washing with ether, is combined with the filtrate and concentrated by evaporation *in vacuo*. The residue yields, upon crystallisation from ether/petroleum ether, 5.0 g of 2 - (*p*-ethoxybenzyl) - 5 - methoxy - 3(2H) - benzofuranone as yellowish crystals, M.P. 92—94°.

b) Analogously to example 1c), 18 g of 2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3(2H)-benzofuranone—which can also be produced analogously to example 1a) and b) starting with 5 - methoxy - 3(2H) - benzofuranone by way of 2 - (*p* - ethoxybenzylidene) - 5-methoxy - 3(2H) - benzofuranone (M.P. 148—150° from ethanol)—are reacted with 43 g of bromoacetic acid methyl ester to give the 2 - (*p* - ethoxybenzyl) - 5 - methoxy-3 - benzofuranacetic acid methyl ester (oily).

c) Analogously to example 1d) is obtained from 3.74 g of 2 - (*p* - ethoxybenzyl) - 5-methoxy - 3 - benzofuranacetic acid methyl ester, 2 - [2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuran] - ethanol in the form of oil.

d) The alcohol, obtained according to c), is converted, analogously to example 1e) into the p-toluenesulphonic acid 2 - [2 - (*p*-ethoxybenzyl) - 5 - methoxy - 3 - benzofuranyl] - ethyl ester, M.P. 113—114° (from ether/petroleum ether).

e) Analogously to Example 1 f), 2.4 g of the *p* - toluene - sulphonic acid ester, obtained according to d), are reacted with 10 g of pyrrolidine to give the 1 - [2 - [2 - (*p*-ethoxybenzyl) - 5 - methoxy - 3 - benzofuranyl] - ethyl] - pyrrolidine and the latter is converted into its hydrochloride, M.P. 152—153° (from acetone/ether).

f) Analogously with 10 g of diethylamine, the N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuran]-ethylamine and its hydrochloride are obtained. M.P. 123—124°. (Yield 50% of theory).

EXAMPLE 7.

a) Analogously to example 1a), 45 g of 5 - chloro - 3(2H) - benzofuranone [cp. K. Fries, A. Hasselbach and L. Schröter, Ann. Chem. *405*, 346 (1914)] are condensed with 40.5 g of *p*-ethoxybenzaldehyde to give the 2 - (*p* - ethoxybenzylidene) - 5 - chloro-3(2H) - benzofuranone, M.P. 174—175°.

b) 40 g of the above condensation product are hydrogenated, analogously to Example 1b) to give the 2 - (*p* - ethoxybenzyl) - 5 - chloro-3(2H) - benzofuranone, M.P. 77—78° (from ether).

c) Analogously to Example 1c) 19 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3(2H)-benzofuranone are reacted with 43 g of bromoacetic acid methyl ester to give the 2 - (*p*-ethoxybenzyl) - 5 - chloro - 3 - benzofuran-

acetic acid methyl ester (oily).

d) Analogously to Example 1d), 3.8 g of the reaction product of c) are reduced to the crude 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran] - ethanol.

e) The crude alcohol, obtained in d), is converted analogously to Example 1e) into the *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl ester, M.P. 101—103° (from ether/petroleum ether).

f) The reaction of 2.4 g of the *p*-toluenesulphonic acid ester obtained according to e) with 10 g of pyrrolidine according to Example 1f) yields the 1 - [2 - [2 - (*p* - ethoxybenzyl - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine, the hydrochloride of which, after recrystallisation from acetone/water, melts at 196—197° (yield 1.7 g, 80% of theoretical value).

Example 8

a) Analogously to Example 2, 2.4 g of *p*-toluene-sulphonic acid 2 - [2 - (*p* - ethoxybenzyl) 5 - chloro - 3 - benzofuranyl] - ethyl ester [cp. Example 7a)—e)] are reacted with 0.6 ml of piperidine to give the 1 - [2 - [2-(*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - piperidine, the hydrochloride of which melts after recrystallisation from dioxane/water at 212—213° (yield 1.6 g, 74% theoretical value).

b) In an analogous manner 2.4 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl ester are reacted with dimethylamine to give 1.7 g of N,N - dimethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5-chloro - 3 - benzofuran] - ethylamine hydrochloride, M.P. 160—161° (from acetone) (yield 85% of Theory).

Example 9

Analogously to example 1f), 2.4 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl ester [cp. example 7a)—e)] are reacted with 10 ml of morpholine to give the 4 - [2-[2 - (*p* - ethoxybenzyl) - 5 - chloro - 3-benzofuranyl] - ethyl] - morpholine and its hydrochloride, M.P. 205—206° (from water). Yield 1.9 g, 87% of theoretical value.

Example 10

Analogously to Example 3 is produced, by reaction of 2.4 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro-3 - benzofuranyl] - ethyl ester [cp. Example 7a)—e)] with 10 ml of diethylamine the N-[2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro-3 - benzofuranyl] - ethyl] - diethylamine, the hydrochloride of which, after recrystallisation from acetone/ether, melts at 129—130° (yield 1.8 g, 85% of Theory).

In an analogous manner from *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl)-5 - chloro - 3 - benzofuranyl] - ethyl ester, and 10 ml of di - n - propylamine, is obtained the N - [2 - [2 - (*p* - ethoxybenzyl) - 5-chloro - 3 - benzofuranyl] - ethyl] - di - n-propylamine hydrochloride, M.P. 123—124°.

Example 11

a) The condensation of 36.2 g of 3(2H)-benzofuranone with 40.5 g of *p*-ethoxybenzaldehyde, analogously to example 1a), yields the 2 - (*p* - ethoxybenzylidene) - 3(2H)-benzofuranone, M.P. 135—136° (from ethanol).

b) Analogously to example 1b) is obtained, by hydrogenation of 36 g of the above condensation product, the oily 2 - (*p* - ethoxybenzyl) - 3(2H) - benzofuranone.

c) From 16.2 g of 2 - (*p* - ethoxybenzyl)-3(2H) - benzofuranone and 43 g of bromoacetic acid methyl ester is obtained, analogously to example 1c), the 2 - (*p* - ethoxybenzyl) - 3 - benzofuranacetic acid methyl ester as an oil.

d) The reduction of 3.5 g of the methyl ester, obtained according to c), analogously to example 1d), yields the crude 2 - [2 - (*p*-ethoxybenzyl) - 3 - benzofurna] - ethanol.

e) The crude alcohol, obtained according to d), is converted, analogously to example 1e), into the p-toluenesulphonic acid 2 - [2 - (*p*-ethoxybenzyl) - 3 - benzofuranyl] - ethyl ester, M.P. 73—74° (from ether/petroleum ether).

f) By reaction of 2.2 g of the *p*-toluenesulphonic acid ester, obtained according to e), with 30 ml of a saturated solution of dimethylamine in dimethylformamide, analogously to example 5, is obtained the N,N-dimethyl - 2 - [2 - (*p* - ethoxybenzyl) - 3-benzofuran] - ethylamine, and from that its hydrochloride, M.P. 171—173° (from acetone/ether). Yield 1.6 g, 89% of theoretical value.

Example 12

Analogously to example 3, 2.2 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl] - ethyl ester [cp. example 1a)—e)] are reacted with 10 ml of diethylamine to give the N,N - diethyl - 2-[2 - (*p* - ethoxybenzyl) 3 - benzofuran]-ethylamine. From the crude base are obtained 1.5 g (77% of theoretical value) of hydrochloride, M.P. 158—161° (from acetone/ether).

Example 13

Analogously to example 1f) 2.2 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl] - ethyl ester [cp. example 11a)—e)] are reacted with 10 ml of pyrrolidine to give the 1 - [2 - [2 - (*p*-ethoxybenzyl) - 3 - benzofuranyl] - ethyl]-pyrrolidine, the hydrochloride of which, after recrystallisation from acetone/ether, melts at 193—196°. Yield 1.6 g, 83% of theoretical value.

EXAMPLE 14

2.2 g of *p*-toluenesulphonic acid 2 - [2-(*p* - ethoxybenzyl) 3 - benzofuranyl] - ethyl ester [cp. example 11a)—e)] are reacted with 10 ml of piperidine, analogously to example 1f), to give the 1 - [2 - [2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl] - ethyl] - piperidine. The hydrochloride of this base melts at 194—196° (from acetone/ether). Yield 1.7 g, 85% of theoretical value.

EXAMPLE 15

From 2.2 g of *p*-toluenesulphonic acid 2-[2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl]-ethyl ester [cp. example 11a)—e)] and 10 ml of morpholine is obtained, analogously to example 4, the 4 - [2 - [2 - (*p* - ethoxybenzyl)-3 - benzofuranyl] - ethyl] - morpholine and from that is obtained the hydrochloride, M.P. 189—192° (from acetone/ether). Yield 1.8 g, 90% of theoretical value.

EXAMPLE 16

a) 3.4 g of 2 - (*p* - ethoxybenzyl) - 5-methyl - 3 - benzofuranacetic acid methyl ester [cp. example 1a)—c)] are heated with 16 g of dimethylamine in a closed vessel for 24 hours to 110°. The reaction mixture is then transferred to a flask and the dimethylamine evaporated off. The crystallisation of the residue from acetone yields 1.9 g of N,N,5-trimethyl - 2 - (*p* - ethoxybenzyl) - 3 - benzofuranacetamide as colourless crystals, M.P. 167—168°.

The following are produced analogously: With 3.24 g of 2 - (*p* - ethoxybenzyl) - 3-benzofuranacetic acid methyl ester [cp. example 11a)—c)] is produced the N,N - dimethyl - 2 - (*p* - ethoxybenzyl) - 3 - benzofuranacetamide, M.P. 82—84° (from ether/petroleum ether); with 3.6 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranacetic acid methyl ester [cp. example 7a)—c)] is produced the N,N - dimethyl - 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran - acetamide, M.P. 103—105° (from ether/petroleum ether).

b) 0.5 g of lithium aluminium hydride are suspended, while stirring, in 50 ml of absolute ether and refluxed to boiling. A solution of 0.25 g of N,N5 - trimethyl - 2 - (*p* - ethoxybenzyl) - 3 - benzofuran - acetamide in 25 ml of absolute ether is then slowly added dropwise and the mixture refluxed, while stirring, for a further 24 hours at boiling temperature. The reaction mixture is then carefully decomposed, while cooling with ice, with concentrated hydrochloric acid, an addition is made of 20 ml of a semi-saturated solution of potassium sodium tartrate (Seignette's salt) and then of concentrated aqueous ammonia solution until an alkaline reaction to litmus is obtained, the mixture shaken and the ether layer removed. The ether phase, washed with water and dried over sodium sulphate yields, after concentration by evaporation, ca. 0.212 g of crude base. By dissolving the latter in acetone and adding ethereal hydrogen chloride solution, crude, oily hydrochloride is obtained, which crystallises upon trituration. After recrystallisation from acetone are obtained 0.215 g of N,N - dimethyl - 2 - [2 - (*p*-ethoxybenzyl) - 5 - methyl - 3 - benzofuran]-ethylamine hydrochloride, M.P. 156—158°. Yield 80% of theoretical value.

The following are obtained analogously, using the same amounts of the corresponding dimethylacetamides:

the N,N - dimethyl - 2 - [2 - (*p* - ethoxybenzyl) - 3 - benzofuran] - ethylamine hydrochloride, M.P. 171—173° (from acetone) and

the N,N - dimethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran]-ethylamine hydrochloride, M.P. 160—161° (from acetone).

EXAMPLE 17

a) 23.5 g of 2(3H) - benzofuranone and 57 g of bromoacetic acid methyl esrer are dissolved together in 250 ml of absolute benzene and slowly added dropwise to a mixture, being vigorously stirred and consisting of 30 g of zinc wool, 0.1 g of mercury(II) chloride and 100 ml of boiling benzene. The zinc is practically fully dissolved after 3 hours and the reaction mixture is thereupon refluxed at boiling temperature for a further 4 hours. It is then cooled to room temperature and decomposed with 200 ml of 2N sulphuric acid. The two-phase mixture is stirred for a further hour at room temperature, the benzene layer removed, washed until neutral, dried over sodium sulphate and concentrated by evaporation. Distillation of the residue under 10 Torr yields 4.0 g of 3-benzofuranacetic acid methyl ester as colourless oil, B.P. 138—145°/10 Torr. (Yield 12% of theoretical value).

The 5 - methyl - 3 - benzofuranacetic acid methyl ester, B.P. 150°/11 Torr, is obtained analogously.

b) 3.9 g of 3-benzofuranacetic acid methyl ester, dissolved in 10 ml of absolute tetrahydrofuran, are added dropwise, while stirring, to a suspension of 1.5 g of lithium aluminium hydride in 30 ml of absolute tetrahydrofuran and refluxed for 3 hours. The mixture is thereupon cooled with ice and decomposed with dilute hydrochloric acid. After the addition of 10 ml of semi-saturated solution of potassium sodium tartrate (Seignette's salt) and neutralisation with concentrated aqueous ammonia solution, the tetrahydrofuran is evaporated off under vacuum and the obtained mixture, after being diluted with water, repeatedly extracted with ether. The ether extracts, washed until neutral and dried over sodium sulphate, are filtered through 20 g of neutral aluminium oxide, Woelm activity stage III, and eluted

with ether. Filtrate and extract are combined and concentrated by evaporation, whereby 2.7 g of crude 2 - [3 - benzofuran] - ethanol are obtained (yield 89%).

c) The crude 2 - [3 - benzofuran]-ethanol, obtained according to b), is dissolved in 10 ml of absolute pyridine and the solution cooled to −10°. 4.0 g of *p*-toluenesulphochloride are added in portions in such a manner that the temperature does not exceed −5°. The mixture is allowed to stand for ca. 15 hours at 0°, then poured into ice-water and the precipitated oil triturated. Crystallisation occurs after some time. Recrystallisation from ethanol yields 4.0 g of *p*-toluenesulphonic acid 2 - (3 - benzofuranyl) - ethyl ester as crystals, M.P. 58—59°. (Yield 76% of theoretical value).

d) 3.3 g of *p*-toluenesulphonic acid 2 - (3-benzofuranyl) - ethyl ester and 6.0 g of liquid ammonia are heated in a closed vessel for 4 hours to 100°. After evaporating off the ammonia, the reaction mixture is taken up with ether and 3 ml of 10% potassium carbonate solution. The ether phase is separated and dried over sodium sulphate and concentrated by evaporation. 1.4 g of 2 - (3-benzofuran) - ethylamine are obtained as an almost colourless oil (yield 93% of theoretical value).

e) To 1.0 g of *p*-ethoxybenzoyl chloride is added at 0°, a solution of 1.0 g of 2 - (3-benzofuran) - ethylamine in 5 ml of absolute pyridine. After standing at room temperature for 4 hours, the reaction mixture is poured into water and extracted with ether. The ether phase is washed with dilute hydrochloric acid and then with water, dried over sodium sulphate and concentrated by evaporation. 1.5 g of N - [2 - (3 - benzofuranyl) - ethyl]-*p* - ethoxy - benzamide thereby precipitate as colourless crystals, M.P. 125—126°. (Yield 70% of theoretical value).

f) 1.0 g of phosphorus pentoxide and 2.0 g of phosphorus oxychloride are added to 0.5 g of N - [2 - (3 - benzofuranyl) - ethyl]-*p* - ethoxy - benzamide in 40 ml of toluene. The mixture is refluxed for 4 hours to boiling while vigorously stirring. It is then cooled with ice, carefully decomposed by addition of a little water and the mixture transferred to a separating funnel by rinsing the reaction vessel with 40 ml of chloroform. The organic phase yields, after being washed with water until neutral, dried with sodium sulphate and concentrated by evaporation *in vacuo*, 0.48 g of residue. By crystallisation of the latter from acetone, 0.45 g of yellowish 1 - (*p* - ethoxyphenyl) - 3,4 - dihydrobenzofuro[2,3 - c]-pyridine hydrochloride, M.P. 150—153°, are obtained, yield 85% of theoretical value.

g) 0.2 g of 1 - (*p* - ethoxyphenyl) - 3,4-dihydrobenzofuro[2,3 - c]pyridine hydrochloride are heated in 5 ml of diethylene glycol under nitrogen with 0.6 ml of hydrazine hydrate and 0.5 g of sodium hydroxide for one hour to 200°. The reaction mixture is allowed to cool, poured into water and repeatedly extracted with ether. The combined ether solutions, washed with water and dried over sodium sulphate yield, after being concentrated by evaporation, 0.2 g of crude 2-[2 - (*p* - ethoxybenzyl) - 3 - benzofuran]-ethylamine as a yellowish oil.

h) The crude amine, obtained according to g), is refluxed with a mixture of 1 ml of concentrated formic acid and 1 ml of 37% formaldehyde solution for 24 hours. The reaction solution is then cooled, adjusted to pH 8—9 by addition of sodium carbonate solution and extracted with ether. The ether solution, washed until neutral with water and dried over sodium sulphate, is concentrated by evaporation and the residue chromatographed on a column prepared with 5.0 g of neutral aluminium oxide, Woelm activity stage III. The extract obtained with benzene is concentrated by evaporation, dissolved in ether and some acetone and to this solution is added a slight excess of ethereal hydrogen chloride solution. The precipitated N,N - dimethyl-2 - [2 - (*p* - ethoxybenzyl) - 3 - benzofuran]-ethylamine hydrochloride crystallises upon being triturated. M.P. 171—173° after recrystallisation from acetone/ether.

i) 5 - Methyl - 3 - benzofuran - acetic acid is prepared after B. B. Dey and K. Radhabai, J. Ind. Chem. Soc. *11* 635 (1934). 15.4 g of 5 - Methyl - 3 - benzofuran - acetic acid are added to a suspension of 9.0 g of lithium aluminium hydride in 200 ml of absolute diethyl ether and the resulting mixture is boiled under reflux for 4 hours with stirring. The reaction mixture is then cooled with ice and decomposed by the addition, dropwise, of 35 ml of water and 7.5 ml of 30% sodium hydroxide solution. The granular precipitate is removed by filtration from the ether solution and it is washed with ether. After the removal by distillation of the ether there remain 14.0 g of 2 - (5 - methyl - 3-benzofuran) - ethanol as a colourless oil. Yield 97% of Theory.

Analogously to c) is obtained by the reaction of the preceding alcohol (14 g) with 14 g of *p*-toluenesulphochloride in 60 ml of pyridine, 24 g of *p*-toluenesulphonic acid 2-(5-methyl - 3 - benzofuran) - ethyl ester as a yellowish oil, (yield 91% of Theory), and from this, after reaction with 124 g of liquid ammonia at 100° in a high pressure vessel, analogously to d), 9.7 g of 2 - (5 - methyl-3 - benzofuran) - ethylamine as a colourless oil. Yield 76% of theory.

Analogously to e) is obtained from 9.7 g of the preceding amine and 12.0 g of *p*-ethoxybenzoyl chloride 15.2 g of N - [2 - (5-methyl - 3 - benzofuranyl) - ethyl] - *p*-ethoxybenzamide, M.P. 112—113°. Yield 85% of theory.

Analogously to f) is obtained from 16.0 g of the preceding amide, after treatment with 15.0 g of phosphorus pentoxide and 13 ml of phosphorus oxychloride in 300 ml of toluene and crystallisation from acetone, 16.5 g of 1 - (*p* - ethoxyphenyl) - 6 - methyl - 3,4-dihydro - benzofuro[2,3 - c] - pyridine-hydrochloride, M.P. 170—171°. Yield 98% of theory.

EXAMPLE 18

i) a) 270 g of tin tetrachloride are slowly added dropwise, while stirring, to a solution of 25.5 g of 2 - (*p* - ethoxybenzyl)-benzofuran and 9.0 g of acetyl chloride in 40 ml of carbon disulphide. The reaction mixture is further stirred for 19 hours at room temperature, then decomposed, while cooling with ice, by the addition of water and the mixture extracted with chloroform. The chloroform solution is washed until neutral, dried over sodium sulphate and concentrated by evaporation *in vacuo*. 33 g of a brown oil remain, which are chromatographed on 500 g of neutral aluminium oxide, Woelm activity stage III, in the system benzene/petroleum ether (1 : 1 v/v). The first three fractions (total volume 1.5 litres) yield, after concentration by evaporation from ether/petroleum ether, 13.0 g of 2 - (*p* - ethoxybenzyl) - 3 - acetyl-benzofuran, M.P. 71—72° (yield 42% of theoretical value). After recrystallisation from petroleum ether, the product melts at 73—74°. From the subsequent fractions (elution agent benzene/ether (9 : 1 v/v) are obtained, by crystallisation from ether, 3.6 g of 2 - (*p*-hydroxybenzyl) - 3 - acetyl - benzofuran, M.P. 148°.

b) 5.0 g of 2 - (*p* - ethoxybenzyl) - 3-acetyl - benzofuran are dissolved in 50 ml of carbon tetrachloride and to this is firstly added, while stirring, 0.1 g of dibenzoyl peroxide. While cooling with ice, 3.0 g of bromine, dissolved in 50 ml of carbon tetrachloride, are added dropwise within one hour. The reaction solution is then allowed to stand for a further hour at room temperature. After washing with water and sodium bicarbonate solution, drying over sodium sulphate and concentrating by evaporation, is obtained the 2 - (*p* - ethoxybenzyl) - 3 - bromoacetyl-benzofuran as a brown oil, which is directly further used.

c) The crude bromine ketone of b) is dissolved in 50 ml of ether, 5 ml of pyrrolidine are added and the solution is refluxed for one and a half hours. The reaction mixture is then washed neutral with water, dried with sodium sulphate and concentrated by evaporation. The residue is taken up in benzene to remove volatile, adhering pyrrolidine, and concentrated by evaporation *in vacuo*. The crude base remaining is dissolved in ether and to the solution is added a slight excess of ethereal hydrogen chloride solution. The precipitated 2 - (*p* - ethoxybenzyl) - 3 - (1-pyrrolidinyl - acetyl) - benzofuran hydrochloride is crystallised from acetone/ether, whereby 3.4 g are obtained. M.P. 182—187° (with decomposition). Yield 51% of theoretical value).

d) 0.50 g of 2 - (*p* - ethoxybenzyl) - 3-(1 - pyrrolidinyl - acetal) - benzofuran hydrochloride are suspended in a little water. To this is added a slight excess of ammonia and the liberated base extracted with ether. After drying over magnesium sulphate, the ether solution of the base is concentrated to a volume of 3 ml and at 0° a mixture of 5 ml of boron trifluoride etherate and 5 ml of tetrahydrofuran is added dropwise. A white precipitate thereby forms which immediately goes into solution again. After allowing the solution to stand at room temperature for 30 minutes, 2 ml of 1.8-molar diborane solution in tetrahydrofuran are added (slight evolution of gas) and ether is distilled off until the temperature of the reaction mixture is 55°. The reaction mixture is then refluxed for half an hour, a further addition made of 1 ml of diborane solution with refluxing proceeding for a further half hour. After concentrating the reaction mixture by evaporation *in vacuo*, the residue is decomposed with methanol and again concentrated by evaporation. Water and ice are added to the residue and the mixture made alkaline with ammonia. The precipitate base is extracted with ether, the ether solution washed with water, dried over sodium sulphate, filtered through 5 g of neutral aluminium oxide, Woelm activity stage III, and the aluminium oxide subsequently washed with ether. Filtrate and extract are combined and a small excess of ethereal hydrogen chloride solution is then added. The precipitated crude 1 - [2 - [2 - (*p* - ethoxybenzyl) - 3-benzofuranyl] - ethyl] - pyrrolidine hydrochloride is separated and recrystallised from acetone/ether, whereby 0.40 g of colourless needles, M.P. 193—196°, are obtained. (Yield 83% of theoretical value).

ii) 122 g of salicylaldehyde are added to a solution of 62 g of potassium hydroxide in 1,800 ml of ethanol. 250 g of *p*-ethoxyphenacyl bromide are added to the solution and it is stirred for 5 hours at boiling point under reflux. The thus formed potassium bromide is then filtered off and the filtrate evaporated under vacuum. During the evaporation the product crystallises out. After recrystallisation from ethanol 170 g of 2 - *p* - ethoxybenzoyl-benzofuran is obtained, M.P. 98—101° (yield 60% of Theory). 100 g of 2 - *p* - ethoxy-benzoyl - benzofuran are dissolved in 250 ml of diethylene glycol, mixed with 92 g of hydrazine hydrate and the mixture heated at boiling point for 15 minutes. The mixture is left to cool and after the addition of 83 g of potassium hydroxide it is heated in a distillation apparatus for 3½ hours at 200°. After cooling the reaction mixture is poured into

ice and acidified with 1200 ml of 2N-hydrochloric acid. The product is extracted with benzene, the extract washed with water, dried over sodium sulphate, evaporated *in vacuo* at 60° and the residual oil is distilled *in vacuo*. 71 g of 2 - *p* - ethoxybenzyl - benzofuran, B.P. 214—216° at 13 Torr, are obtained. (Yield 75% of Theory.)

Similarly are obtained from

10 g 5-methylsalicyl aldehyde
24 g 5-chloro-salicyl aldehyde
20 g 5-methoxysalicyl aldehyde

After crystallisation from ethanol

12 g 2 - (*p* - ethoxybenzoyl) - 5 - methylbenzofuran, M.P. 100—101°, (yield 59% of Theory)
24.5 g 2 - (*p* - ethoxybenzoyl) - 5 - chlorobenzofuran, M.P. 129—131° (yield 53% of Theory)
31.0 g 2 - (*p* - ethoxybenzoyl) - 5 - methoxybenzofuran, M.P. 113—115° (yield 79% of Theory),

and from these, after reduction with hydrazine hydrate, vacuum distillation in a particle tube and crystallization from methanol

8.8 g 2 - (*p* - ethoxy - 5 - methylbenzofuran, M.P. 38—39° (yield 77% of Theory)
13 g 2 - (*p* - ethoxybenzyl) - 5 - chlorobenzofuran, M.P. 48—49° (yield 56% of Theory)
16 g 2 - (*p* - ethoxybenzyl) - 5 - methoxybenzofuran, M.P. 52—53° (yield 54% of Theory)

e) To a solution of 8.5 g of 2 - (*p* - ethoxybenzyl) - 5 - methylbenzofuran and 2.4 g of acetyl chloride in 50 ml of carbon disulphide, 3.3 ml of titanium tetrachloride are added dropwise slowly and with stirring. The reaction mixture is stirred for a further 19 hours at room temperature, water is then added with ice cooling, and the mixture is extracted with chloroform. The chloroform solution is washed neutral, dried over sodium sulphate and evaporated *in vacuo*. The residual oil precipitates directly from methanol as crystals. After recrystallisation of these crystals from ether, 8.5 g of 2 - (*p* - ethoxybenzyl)-5 - methyl - 3 - acetylbenzofuran, M.P. 73—74° is obtained (yield 76% of Theory).

In an analogous manner is obtained from 13 g of 2 - (*p* - ethoxybenzyl) - 5 - chlorobenzofuran, after reaction with 3.4 g of acetyl chloride and 4.75 ml of titanium tetrachloride and crystallisation of the isolated crude product from methanol, 8.0 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - acetyl - benzofuran, M.P. 93—95°, (yield 53% of Theory).

Analogously to b) is obtained from 2.83 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3-acetylbenzofuran and 0.55 ml of bromine, 2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - bromoacetyl - benzofuran, which gives after crystallisation from ether, 2.6 g of crystals, M.P. 95—96° (yield 73% of Theory).

Analogously to b) is obtained from 3.28 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3-acetyl - benzofuran and 0.57 ml of bromine, 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3-bromo - acetyl - benzofuran, which gives after crystallisation from ether, 3.7 g of crystals, M.P. 107—109° (yield 91% of theory).

Analogously to c) is obtained from 1 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3-bromoacetyl - benzofuran and 1.0 ml of pyrrolidine after isolation of the crude base, conversion of the same into its hydrochloride and crystallisation from acetone/ether, 0.50 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3-(1 - pyrrolidinyl - acetyl) - benzofuran - hydrochloride, M.P. 162—165° (decomposition). Yield 47% of Theory. Also, with 1.0 ml of piperidine, after crystallisation from water, 0.60 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl-3 - (1 - piperidinyl - acetyl) - benzofuran hydrochloride, M.P. 172—174° (with decomposition). Yield 67% of Theory.

Analogously to c) is obtained from 2.7 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3-bromo - acetyl - benzofuran and 3 ml of pyrrolidine, after crystallisation from acetone, 1.6 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro-3 - (1 - pyrrolidinyl - acetyl) - benzofuran hydrochloride, M.P. 186—190° (with decomposition). Yield 56% of Theory. Also, with 3 ml of diethylamine, after crystallisation from acetone/ether, 1.8 g of 2 - (*p* - ethoxybenzyl)-5 - chloro - 3 - (N,N - diethylamino - acetyl)-benzofuran hydrochloride, M.P. 150—152 (decomposition). Yield 63% of Theory.

Analogously to d) is obtained from 0.5 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3-(1 - pyrrolidinyl - acetyl) - benzofuran hydrochloride, after liberation of the base and treating the same with 5 ml of borontrifluoride etherate and 3 ml of 1.8 molar diborane solution in tetrahydrofuran after final processing and crystallisation from acetone 0.35 g of 1-[2 - [2 - (*p* - ethoxy - benzyl) - 5 - methyl-3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 167—169° (yield 72% of Theory). Also is obtained from 0.5 g of 2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - (1-piperidinyl - acetyl) - benzofuran - hydrochloride, after crystallisation from methanol/acetone, 0.26 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl]-ethyl] - piperidine hydrochloride, M.P. 192—193° (yield 54% of Theory).

Analogously to d) is obtained from 1.0 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - (1 - pyrrolidinyl - acetyl) - benzofuran hydrochloride, after liberation of the base and treatment of the same with 10 ml of boron tri-

fluoride etherate and 6 ml of 1.8 molar diborane solution in tetrahydrofuran after final processing and crystallisation from acetone, 0.5 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine - hydrochloride, M.P. 196—197° (yield 51% of Theory). Also is obtained from 1.0 g of 2 - (p - ethoxybenzyl) - 5 - chloro - 3 - (N - diethylamino - acetyl) - benzofuran-hydrochloride, after crystallisation from acetone/ether, 0.6 g of N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran] - ethylamine hydrochloride, M.P. 129—130° (yield 62% of Theory).

EXAMPLE 19

a) 26.0 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3(2H) - benzofuranone [cp. example 7 a) and b)] and 67.0 g of bromoacetic acid ethyl ester are dissolved together in 430 ml of absolute benzene and the solution is slowly added dropwise to a mixture of 31.5 g of zinc wool, 0.1 g of mercury(II) chloride and 150 ml of boiling benzene, whereby the mixture is vigorously stirred. Practically all the zinc is dissolved after 3 hours. The reaction mixture is then refluxed, while stirring, for a further 4 hours at boiling temperature. It is then cooled to 0° and stirred for half an hour with 300 ml of 2N sulphuric acid. The benzene layer is then removed, washed neutral, dried over sodium sulphate and filtered through a chromatography column charged with 500 g of neutral aluminium oxide, Woelm activity stage III. After eluting with benzene and concentrating the filtrate and extract by evaporation, 19.7 g of oily 2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranacetic acid ethyl ester are obtained (61% of theoretical value). The ester is obtained from ether/petroleum ether, as colourless crystals, M.P. 83.5—84°. Yield ca. 54% of theory.

b) 19.5 g of 2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranacetic acid ethyl ester are dissolved in 100 ml of tetrahydrofuran and added dropwise, while stirring, to a suspension of 8.9 g of lithium aluminium hydride in 100 ml of tetrahydrofuran and refluxed for 3 hours. The mixture is thereupon cooled to −5° and decomposed by the addition, dropwise, of ethyl acetate. The mixture is then adjusted to pH 3—4 with 2N hydrochloric acid and concentrated at 30° in vacuo. To the concentrate is added a solution of 20 g of potassium sodium tartrate (Seignette's salt) and the mixture is adjusted to pH 8 with concentrated ammonia. After extraction with ether, washing of the ether solution, drying over sodium sulphate and concentration by evaporation, are obtained 18.0 g of oily crude product. This is applied to a chromatography column charged with 600 g of neutral aluminium oxide, Woelm activity stage III, and eluted with benzene. The evaporation residue of the extract is crystallised from ether/petroleum ether, whereby 12.2 g of 2 - [2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuran] ethanol are obtained as colourless crystals, M.P. 96—98°.

c) 12.2 g of the alcohol, obtained according to b), are dissolved in 115 ml of absolute pyridine and the solution cooled to −10°. 22.8 g of *p*-toluenesulphochloride are added in portions in such a manner that the temperature does not exceed −5°. The mixture is allowed to stand for ca. 15 hours at 0° and is then poured into ice-water. The precipitated oil is taken up in chloroform and the solution cleared of adhering pyridine by shaking with 0.5 N hydrochloric acid. The chloroform solution is then washed neutral, dried over sodium sulphate and concentrated by evaporation. By crystallisation of the residue from ether/petroleum ether are obtained 9.0 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranyl] - ethyl ester as colourless crystals, M.P. 112—113°, yield 54% of theoretical value.

d) 2.5 g of the *p*-toluenesulphonic acid ester of c) are refluxed with 30 ml of morpholine for 5 hours with a bath temperature of 110°. The reaction mixture is then completely concentrated by evaporation *in vacuo*, to the residue are added 20 ml of benzene and the reaction mixture is again concentrated by evaporation. This is repeated until all the volatile amine has been expelled. The residue is taken up with water and ether. The ethereal phase is washed with water and then extracted twice. using 5 ml of 1N sulphuric acid each time. The acid extracts are adjusted to pH 9 with concentrated ammonia and the hereby precipitated (oily) base extracted with ether. The ether solution, washed and then dried over sodium sulphate, is concentrated by evaporation, the crude base remaining is dissolved in acetone and to the solution is added a small excess of ethereal hydrogen chloride solution. The precipitated hydrochloride crystallises upon triturating. After recrystallisation from acetone are obtained 1.73 g of 4 - [2 - [2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranyl] - ethyl] - morpholine hydrochloride, M.P. 194—196°.

e) 1.65 g of 4 - [2 - [2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranyl] - ethyl] - morpholine hydrochloride are dissolved in 20 ml of absolute dioxane, to the solution are added 0.17 g of *p*-toluenesulphonic acid and the mixture is refluxed for one hour. The reaction mixture is then concentrated in vacuo at 20°, made alkaline with 2N sodium carbonate solution and repeatedly extracted with ether. The combined ether extracts are washed with water, dried over sodium sulphate and concentrated

by evaporation. The residue is dissolved in ether and a small excess of ethereal hydrogen chloride solution added. The precipitated 4 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - morpholine hydrochloride is crystallised from water, M.P. 205—206°. Yield 1.46 g, 91.5% of theoretical value.

f) Analogously to d) is obtained the 1 - [2 - [2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 196—197° (from acetone/ether).

g) Analogously to Example 10 is obtained, from the *p*-toluene sulphonic acid ester obtained in c) by reaction with diethylamine, the N - [2 - [2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranyl] - ethyl] - diethylamine hydrochloride, M.P. 172—173° (from acetone/ether).

Example 20

a) 2.5 g of p-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranyl] - ethyl ester [cp. example 19 a)—c)] are refluxed with 30 ml of piperidine for 5 hours. Preparation and production of the hydrochloride are carried out analogously to example 19 c). 1.6 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 206—207° are obtained (from acetone/water).

b) 1.60 g of the hydrochloride, obtained according to a), are dissolved in 30 ml of dioxane. 7 ml of saturated ethereal hydrogen chloride solution are added to the solution and the latter refluxed for one hour. The reaction solution is then concentrated in vacuo to a volume of ca. 8 ml. With the addition of water, 1.5 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 212—213°, crystallise.

c) In an analogous manner is obtained from 2.2 g of N - [2 - [2 - (*p* - ethoxybenzyl) - 3-hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranyl] - ethyl] - diethylamine hydrochloride after crystallisation from acetone/ether 2.0 g of N - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - diethylamine hydrochloride, M.P. 129—130°, (Yield 95% of theory) and from 2.0 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 3 - hydroxy - 5 - chloro - 2,3 - dihydro - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, after crystallisation from acetone/ether 1.8 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 196—197°. Yield 94% of theory.

Example 21

a) 3.4 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid methyl ester are refluxed with 12 ml of 1N potassium hydroxide solution and 20 ml of ethanol for 2 hours. The ethanol is evaporated off, the mixture acidified with 2N sulphuric acid, the ether solution, washed and then dried over sodium sulphate, is extracted with ether and concentrated by evaporation, whereby the corresponding crude acid is obtained. By crystallisation from ether/petroleum ether are obtained 2.0 g of pure 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid as colourless needles, M.P. 174—175°. (Yield 60% of theoretical value).

b) In an analogous manner 3.0 g of 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuran - acetic acid ethyl ester are hydrolysed with 12 ml of N-potassium hydroxide solution. After crystallisation from ether/petrol ether 1.57 g of 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuran - acetic acid are obtained, M.P. 122—125°, (yield 64% of theory).

3.2 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran - acetic acid methyl ester are hydrolysed with 12 ml of N - potassium hydroxide solution. After crystallisation from ether/petroleum ether are obtained 2.0 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran - acetic acid: M.P. 156—157°, (yield 65% of theory).

3.0 g of 2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuran - acetic acid methyl ester are hydrolysed with 12 ml of N-potassium hydroxide solution. After crystallisation from ether/petroleum ether are obtained 1.8 g of 2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuran - acetic acid, M.P. 146—148°, (yield 65% of theory).

Example 22

i) a) 18.0 g of 5 - methyl - 3(2H) - benzofuranone and 20.0 g of *p* - isopropoxybenzaldehyde are reacted in 20 ml of ethanol and 1 ml of concentrated hydrochloric acid analogously to example 1 a). After crystallisation from ethanol are obtained 21.0 g of 2 - (*p* - isopropoxybenzylidene) - 5 - methyl - 3(2H) - benzofuranone, M.P. 132—133°. Yield 58% of theoretical value.

b) 20.0 g of the benzylidene compound are hydrogenated, analogously to example 1 b), in 400 ml of dioxane in the presence of 4 g of the therein stated catalyst. Crystallisation of the crude product from ether/petroleum ether yields 12.0 g of 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3(2H) - benzofuranone, M.P. 80—82°. Yield 60% of theoretical value.

c) 10.0 g of 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3(2H) - benzofuranone, 26.2 g of bromoacetic acid ethyl ester and 11.4 g of zinc wool are reacted analogously to example 1 c). After purification on 70 g of neutral aluminium oxide, Woelm activity stage III, 10.0 g of 2 - (*p* - isopropoxybenzyl) - 5 -

methyl - 3 - benzofuranacetic acid ethyl ester are obtained as an oily product. Yield 80% of theoretical value.

d) 12.0 g of 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid ethyl ester are reduced, analogously to example 1 d), with 5.6 g of lithium aluminium hydride. 10.0 g of crude product are obtained and from that, after purification on 300 g of neutral aluminium oxide, Woelm activity stage III, are obtained 7.0 g of 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuran]ethanol as a colourless oil. Yield 66% of theoretical value.

e) 3.5 g of 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuran]ethanol are reacted, analogously to example 1 e) with 6.7 g of *p*-toluenesulphochloride. After crystallisation from ether/petroleum ether are obtained 4.2 g of p - toluenesulphonic acid 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester as colourless crystals, M.P. 110—111°.

f) 4.2 g of *p* - toluenesulphonic acid 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester and 20 ml of pyrrolidine are reacted, analogously to example 1 f). After crystallisation from acetone/ether are obtained 2.9 g of 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 191—192°. Yield 80% of theoretical value.

ii) In an analogous manner 2.0 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester are reacted with 0.6 ml of piperidine. The crude base obtained produces 1.88 g of its crystalline hydrogen sulphate by the addition of 2-sulphuric acid. After recrystallisation from acetone, 1.68 g of 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrogen sulphate are obtained, M.P. 171—172°, (yield 82% of theory), and 2.0 g of *p* - toluenesulphonic acid 2 - [2 - (*p* - isopropoxybenzyl)- 5 - methyl - 3 - benzofuranyl] - ethyl ester are reacted with 10 ml of morpholine to give 4 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - morpholine, the hydrochloride of which melts, after recrystallisation from acetone, at 199—200°, yield 1.44 g, 80% of theory. In a similar manner there is obtained from 2.0 g of the *p*-toluenesulphonic acid ester and 10 ml di-n - propylamine the N,N - dipropyl - 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine, the hydrochloride of which melts after recrystallisation from acetone/ether at 163—164°, yield 1.48 g, 78% of theory.

Example 23

a) 14.8 g of 5 - methyl - 3(2H) - benzofuranone and 13.6 g of anisaldehyde are reacted in 5 ml of ethanol and 1 ml of concentrated sulphuric acid, analogously to Example 1 a). After crystallisation from ethanol, 12.5 g of 2 - *p* - (methoxybenzylidene) - 5 - methyl - 3(2H) - benzofuranone are obtained, M.P. 152°, yield 47% of theory.

b) 12.5 g of the benzylidene compound are hydrogenated analogously to Example 1 b) in 250 ml of dioxane in the presence of 2.5 g of the therein mentioned catalyst. The crystallisation of the crude product from ether/petroleum ether gives 9.5 g of 2 - (*p* - methoxybenzyl) - 5 - methyl - 3(2H) - benzofuranone, M.P. 56—59°, Yield 76% of theory.

c) 9.0 g of 2 - (*p* - methoxybenzyl) - 5 - methyl - 3(2H) - benzofuranone, 26.2 g of bromo-acetic acid ethyl ether and 11.4 g of zinc wool are reacted together analogously to Example 1 c). After purifying on 70 g of neutral aluminium oxide, Woelm activity stage III, 10.0 g of 2 - (*p* - methoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid ethyl ester are obtained as oily product, (yield 89% of theory). IR in substance: 1740 cm^{-1}CO.

d) 10.0 g of 2 - (*p* - methoxybenzyl) - 5 - methyl - 3 - benzofuran - acetic acid ethyl ester are reduced, analogously to Example 1 d), with 5.1 g of lithium aluminium hydride. 9.0 g of crude product are obtained, and after purifying on 160 g of neutral aluminium oxide, Woelm activity stage III, 7.0 g of 2 - [2 - (*p* - methoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethanol are obtained as a colourless oil. (Yield 83% of Theory).

e) 7.0 g of 2 - [2 - (*p* - methoxybenzyl) - 5 - methyl - 3 - benzofuran] ethanol are reacted analogously to Example 1 e) with 15.3 g of *p*-toluenesulphochloride. 6.0 g of crude oily p - toluenesulphonic acid 2 - [2 - (*p* - methoxy - benzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester are obtained, yield 55% of Theory.

f) 6.0 g of *p* - toluenesulphonic acid 2 - [2 - (*p* - methoxy - benzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester and 30 ml of pyrrolidine are reacted together, analogously to Example 1 f). After crystallisation from acetone, 3.0 g of 1 - [2 - [2 - (*p* - methoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride are obtained, M.P. 183—184°, yield 60% of theory.

Example 24

a) 5.0 g of 5 - Methoxy - 3(2H) - benzofuranone [cp. K. von Auwers and P. Pohl, Ann. *405* 281 (1914)] are reacted with 6.0 g of *p* - isopropoxy - benzaldehyde in 5 ml of ethanol and 0.5 ml of concentrated hydrochloric acid. The separated crude product is recrystallised from ethanol. 6.6 g of 2 - (*p* - isopropoxy - benzylidene) - 5 - methoxy - 3(2H) - benzofuranone are obtained as yellow needles, M.P. 103—104°, yield 69% of theory.

b) 6.5 g of 2 - (*p* - isopropoxy - benzylidene) - 5 - methoxy - 3(2H) - benzofuranone

are hydrogenated in 130 ml of dioxane over 0.5 g of catalyst (5% paladium on barium carbonate). 6.4 g of crude 2 - (*p* - isopropoxybenzyl) - 5 - methoxy - 3(2H) - benzofuranone are obtained as an oil, yield 98% of theory. IR in CH_2Cl_2 = 1710cm^{-1}CO.

c) 4.5 g of 2 - (*p* - isopropoxybenzyl) - 5 - methoxy - 3(2H) - benzofuranone are reacted with 11.2 g of bromoacetic acid ethyl ester and 5.0 g of zinc wool in 100 ml of benzene. 4.8 g of oily 2 - (*p* - isopropoxy - benzyl) - 5 - methoxy - 3 - benzofuranacetic acid ethyl ester are obtained, yield 87% of Theory. IR in substance = 1740 cm^{-1}CO.

d) 4.8 g of 2 - (*p* - isopropoxybenzyl) - 5 - methoxy - 3 - benzofuran - acetic acid ethyl ester are reduced, analogously to Example 1d), with 2.2 g of lithium aluminium hydride. 4.5 g of crude product are obtained and from this, after purifying on 50 g of neutral aluminium oxide, Woelm activity stage III, 4.0 g of 2 - [2 - (*p* - isopropoxy - benzyl) - 5 - methoxy - 3 - benzofuran] ethanol are obtained as a colourless oil. Yield 94% of Theory. IR in CH_2Cl_2 = 3610 cm^{-1}OH.

e) 4.0 g of 2 - [2 - (*p* - isopropoxy - benzyl) - 5 - methoxy - 3 - benzofuran] - ethanol are reacted, analogously to Example 1 e), with 7.3 g of *p*-toluenesulphochloride. 3.9 g of crude oily *p* - toluenesulphonic acid 2 - [2 - (*p* - isopropoxy - benzyl) - 5 - methoxy - 3 - benzofuranyl] - ethyl ester are obtained, yield 67% of theory. IR in CH_2Cl_2 = 1360, 1180 cm^{-1}SO.

f) 1.9 g of *p* - toluenesulphonic acid 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methoxy - 3 - benzofuranyl] - ethyl ester are reacted with 10 ml of morpholine, analogously to Example 4. After crystallisation from acetone/ether 1.0 g of 4 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methoxy - 3 - benzofuranyl] - ethyl] - morpholine hydrochloride are obtained, M.P. 125—127°. Yield 55% of theory.

Example 25

a) 63 g of 2 - chloro - 2' - hydroxy - 4',5' - dimethyl - acetophenone [cp. S. S. Tiwari and Brajendra Nath Tripathi, J. Indian Chem. Soc. *33* 214 (1956)] are dissolved in 750 ml of boiling ethanol and mixed with 125 g of sodium acetate. After boiling under reflux for 40 minutes, the mixture is filtered to remove the inorganic salts, the filtrate evaporated and the residue crystallised from aqueous ethanol. 45 g of 5,6 - Dimethyl - 3(2H) - benzofuranone are obtained, M.P. 109—110°. Yield 88% of theory.

b) 45 g of 5,6 - dimethyl - 3(2H) - benzofuranone and 30 g of *p* - ethoxy - benzaldehyde are reacted in 55 ml of ethanol and 3 ml of concentrated hydrochloric acid, analogously to Example 1 a). After crystallisation from ethanol, 50 g of 2 - (*p* - ethoxybenzylidene) - 5,6 - dimethyl - 3(2H) benzofuranone are obtained, M.P. 138—139°. Yield 61% of theory.

c) 44.5 g of 2 - (*p* - ethoxybenzylidene - 5,6 - dimethyl - 3(2H) - benzofuranone are hydrogenated, analogously to Example 1 b), in 900 ml of dioxane and in the presence of 7 g of the therein mentioned catalyst. The crystallisation of the raw product from ether/petrol ether produces 30.0 g of 2 - (*p* - ethoxybenzyl) - 5,6 - dimethyl - 3(2H) - benzofuranone, M.P. 83—84°, yield 67% of theory.

d) 11.0 g of 2 - (*p* - ethoxybenzyl) - 5,6 - dimethyl - 3(2H) - benzofuranone are reacted with 28.8 g of bromoacetic acid ethyl ester and 13.7 g of zinc wool. After purifying on 100 g of neutral aluminium oxide, Woelm activity stage III, 10 g of oily 2 - (*p* - ethoxybenzyl) - 5,6 - dimethyl - 3 - benzofuran - acetic acid ethyl ester are obtained, yield 74% of theory. After recrystallisation from ether/petroleum ether crystals are obtained, M.P. 78—79°.

e) 10.0 g of 2 - (*p* - ethoxybenzyl) - 5,6 - dimethyl - 3 - benzofuran - acetic acid ethyl ester are reduced analogously to Example 1d) with 3.4 g of lithium aluminium hydride. 6.5 g of crude product are obtained and after purifying on 50 g of neutral aluminium oxide, Woelm activity stage III, and crystallisation of the purified product from ether/petroleum ether, 5.3 g of 2 - [2 - (*p* - ethoxybenzyl) - 5,6 - dimethyl - 3 - benzofuran] ethanol are obtained, M.P. 83—85°. Yield 60% of theory.

f) 1.8 g of 2 - [2 - (*p* - ethoxybenzyl) - 5,6 - dimethyl - 3 - benzofuran] - ethanol are reacted, analogously to Example 1 e), with 3.5 g of *p*-toluenesulphochloride. After crystallisation of the crude product from ether, 2.1 g of *p* - toluenesulphonic acid 2 - [2 - (*p* - ethoxy - benzyl) - 5,6 - dimethyl - 3 - benzofuranyl] - ethyl ester are obtained, M.P. 142—143°. Yield 79% of Theory.

g) 2.1 g of *p* - toluenesulphonic acid 2-[2 - (*p* - ethoxy - benzyl) - 5,6 - dimethyl - 3 - benzofuranyl] - ethyl ester and 11 ml of pyrrolidine are reacted analogously to Example 1 f). After crystallisation from acetone/ether 1.8 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5,6 - dimethyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrogen sulphate are obtained, M.P. 103—104°. Yield 86% of Theory.

Example 26.

a) 7.0 g of [4 - nitro - 2 - (ethoxycarbonyl)-phenoxy] - acetic acid ethyl ester [cf. W. A. Jacobs and M. Heidelberger, J.A.C.S. *39* 2188 (1917)] M.P. 75—76°] are added in portions to 1.12 g of 50% sodium hydride dispersion in 50 ml of benzene with stirring at 80°. Upon the dissolving of the sodium hydride, a thicker slurry if formed. After the end of this reaction, 25.6 ml of a 37% solution of *p* - ethoxy - benzyl bromide in benzene are slowly added and the reaction proceeds from this point analogously to Example 6. The thus

crude 2 - (*p* - ethoxybenzyl) - 5 - nitro - 3(2H) - oxo - 2 - benzofuran - carboxylic acid ethyl ester gives, after crystallisation from methanol, 1.4 g of crystals, M.P. 123—124°, yield 16% of theory.

b) 1.0 g of 2 - (*p* - ethoxybenzyl) - 5 - nitro - 3(2H) - oxo - 2 - benzofuran - carboxylic acid ethyl ester are heated to boiling under reflux for 1½ hours with 27ml of 0.1N sodium hydroxide. After cooling, the solution is made acid to Congo red with dilute hydrochloric acid and extracted with ether. The ether extract is washed neutral, dried over sodium sulphate and evaporated. Crystallisation of the residue from methanol produces 0.25 g of 2 - (*p* - ethoxybenzyl) - 5 - nitro - 3(2H) - benzofuranone, M.P. 109—111°.

c) 0.4 g of 2- (*p* - ethoxybenzyl) - 5 - nitro - 3(2H) - benzofuranone are reacted analogously to Example 1 c) with 2.4 g of bromoacetic acid ethyl ester and 1.0 g of zinc wool. After purifying on 20 g of neutral aluminium oxide, Woelm activity stage III, 0.37 g of 2 - (*p* - ethoxybenzyl) - 5 - nitro - 3 - benzofuran - acetic acid ethyl ester are obtained as a yellowish oil. Yield 76% of theory. IR in CH_2Cl_2 = 1735 cm^{-1}CO; 1525, 1330$cm^{-1}NO_2$.

d) 0.37g of 2 - (*p* - ethoxybenzyl) - 5 - nitro - 3 - benzofuran - acetic acid ethyl ester are heated to boiling point under reflux for 1½ hours with 5 ml of 0.7 molar diborane solution in tetrahydrofuran. The excess diborane is decomposed by the addition of methanol and to the resulting solution are added a few drops of a hydrogen chloride solution in methanol and the resulting mixture is heated to boiling under reflux for ½ hour. The solvents and the boric acid methyl ester produced as by-product are removed by evaporation *in vacuo* and the residue is taken up in ether and water. The ether extract is washed neutral and dried over sodium sulphate. After the evaporation of the ether, 0.33 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - nitro - 3 - benzofuran] ethanol are obtained as a yellowish oil. Yield 97% of theory. IR in CH_2Cl_2 = 3600 cm^{-1}OH; 1525, 1330 $cm^{-1}NO_2$.

e) 0.33 g of 2 - [2 - (*p* - ethoxybenzyl)- 5 - nitro - 3 - benzofuran] ethanol are reacted analogously to Example 1 e) with 0.7 g of *p*-toluene sulphochloride. 0.30 g of the crude oily *p* - toluenesulphonic acid 2 - [2 - (*p* - ethoxy - benzyl) - 5 - nitro - 3 - benzofuranyl] - ethyl ester are obtained. Yield 63% of Theory. IR in CH_2Cl_2 = 1360, 1180 cm^{-1}SO.

f) 0.30 g of *p* - toluenesulphonic acid 2 - [2 - (*p* - ethoxy - benzyl) - 5 - nitro - 3 - benzofuranyl] - ethyl ester are reacted analogously to Example 1 f) with 1.0 ml of pyrrolidine. After crystallisation from acetone, 0.1 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - nitro - 3 - benzofuranyl] - ethyl] - pyrrolidine - hydrochloride are obtained, M.P. 199—201°. Yield 40% of theory.

Example 27

0.32 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid are dissolved in 5 ml of absolute tetrahydrofuran. To this solution are added 0.5 ml of thionyl chloride and the solution is refluxed for 2 hours to boiling. The solution is then concentrated by evaporation *in vacuo*, 5 ml of absolute benzene are added and the solution again concentrated by evaporation, whereby adhering thionyl chloride is removed. The obtained crude 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid chloride is dissolved in 5 ml of absolute benzene and a solution of 1.0 ml of piperidine in 5 ml of benzene added dropwise. An exothermic reaction thereby occurs with precipitation of piperidine hydrochloride. After the addition is completed, the solution is boiled for a short time and filtered hot. The filtrate is washed with dilute hydrochloric acid and water, dried over sodium sulphate and concentrated by evaporation. Crystallisation of the residue from ether/petroleum ether yields 0.25 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid piperidide, M.P. 97—98°.

0.16 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid piperidide are dissolved in 25 ml of ether and added dropwise to a stirred suspension of 0.5 g of lithium aluminium hydride in 30 ml of ether. The mixture is subsequently refluxed, while stirring, for 20 hours. The mixture is then cooled with ice and decomposed by adding dilute hydrochloric acid dropwise. To the mixture is added a solution of 5 g of potassium sodium tartrate in 20 ml of water. The mixture is adjusted to pH 8—9 by the addition of ammonia solution and shaken. The ethereal phase is washed with water, dried over sodium sulphate and concentrated by evaporation. The obtained crude 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine is converted into its hydrochloride. By this means are obtained 0.15 g, M.P. 192—193°, yield 89% of theoretical value.

In an analogous manner is obtained from 0.32 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid and 0.5 ml of thionyl chloride, the corresponding acid chloride and from the latter is obtained, after treatment with 1.0 ml of diethylamine and final processing, 0.33 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid diethylamide as colourless oil, yield 87% of theoretical value, IR in CH_2Cl_2 = 1640 cm^{-1} CO—; and from 0.25 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid diethylamide is obtained, after reduction with 0.77 g of lithium aluminium hydride and conversion

of the crude base into the hydrochloride, after crystallisation from acetone/ether, 0.20 g of 2 - (*p* - ethoxybenzyl) - 3 - [2 - (1 - diethylamino) - ethyl] - 5 - methyl - benzofuran hydrochloride, M.P. 139—140°. Yield 75% of theoretical value.

EXAMPLE 28

0.25 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid diethylamide is dissolved in 10 ml of a 0.7-molar solution of diborane in tetrahydrofuran and the solution is allowed to stand for 20 hours at room temperature. The excess diborane is decomposed with methanol, the solution is made clearly acid by addition of methanolic hydrochloric acid and refluxed at boiling for half an hour. The solvent and the boric acid methyl ester, formed as by-product, are removed by concentrating by evaporation *in vacuo*. The residue is taken up in water and ether, ammonia is added until the pH of the aqueous phase is about 9 and the base extracted with ether. The ether extract is washed with water, dried over sodium sulphate and concentrated by evaporation. The obtained crude base is taken up in ether and acetone, the hydrochloride precipitated by addition of ethereal hydrochloric acid and recrystallised from acetone. 0.12 g of 2 - (*p* - ethoxybenzyl)-3 - [2 - diethylamino) - ethyl] - 5 - methylbenzofuran hydrochloride are obtained, M.P. 139—140°. Yield 45% of theoretical value.

In an analogous manner are obtained from 0.2 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid piperidide, after reduction with 10 ml of a 0.7-molar solution of diborane in tetrahydrofuran and conversion of the isolated crude base into the hydrochloride, 0.14 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 192—193°, yield 66% of theoretical value, 0.40 g of 2 - (p - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid pyrrolidide are reduced with 20 ml of a 0.7-molar solution of diborane in tetrahydrofuran and processed. By this means are obtained 0.21 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 167—169°. Yield 51% of theoretical amount.

The pyrrolidide required as starting material is produced as follows:

0.5 g of oily 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid methyl ester (racemate A) dissolved in 5 ml of benzene and to this are added 5 ml of pyrrolidine. After refluxing for 20 hours, the solution is concentrated by evaporation *in vacuo* and the residue crystallised from ether. 0.4 g of 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid pyrrolidide are obtained, M.P. 142—143°. Yield 73% of theoretical value.

EXAMPLE 29A

a) 2.3 g of *p* - toluene sulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester are reacted with 10 ml of propylamine to give the N - propyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine. The hydrochloride of the latter melts, after recrystallisation from methanol/ether, at 160—162°; yield 1.5 g (80% of theoretical value).

b) 0.75 g of N - propyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine hydrochloride are converted, by shaking with 2N soda solution and ether, into the base which, after washing of the ether extract, drying and concentration by evaporation, is obtained as colourless oil. This is taken up in 20 ml of ether, 0.25 ml of pyridine and 0.25 ml of propionic acid chloride are added and the solution is then allowed to stand for 4 hours. After washing with dilute hydrochloric acid and water, the ethereal solution is dried over sodium sulphate and concentrated by evaporation *in vacuo*. By this means are obtained 0.73 g of N - propyl N - [2 - [2-(*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran]ethyl]propionic acid amide as colourless oil; yield 90% of theoretical value. IR in CH_2Cl_2 = 1640 cm^{-1} CO.

Analogously to example 27 are obtained from 0.70 g of N - propyl N - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethyl]propionic acid amide, after reduction with 2.0 g of lithium aluminium hydride and conversion of the crude base into the hydrochloride, 0.65 g of N,N - dipropyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine hydrochloride, M.P. 106—108°. Yield 86% of theoretical value.

EXAMPLE 29B

3.3 g of 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid were reacted with 5.16 ml of thionyl chloride, to form the acid chloride and from this, after reaction with 10 ml of piperidine and after crystallisation from ether/petroleum ether, 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid piperidide, M.P. 81—82°, was obtained. Yield 3.75 g, 95% of theoretical value; and with 10 ml of di - n - propylamine is obtained the oily N,N - dipropyl - 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofurnacetic acid amide. Yield 3.8 g, 97% of theoretical value; and from 10 ml of pyrrolidine are obtained after crystallisation from ether/petroleum/ether 3.44 g of the 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuran - acetic acid pyrrolidide, M.P. 101—103°. Analogously to example 27 are obtained from 3.75 g of 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid piperidide, after reduction with 10 g of lithium aluminium hydride and conversion of the crude base into the hydrogen sulphate—and after crystallisation from acetone—3.55 g of 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 -

benzofuranyl] - ethyl] - piperidine hydrogen sulphate, M.P. 171—172° (yield 79% of theoretical value); and in the same manner, from 3.8 g of N,N - dipropyl - 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid—after crystallisation from acetone/ether, the N,N - dipropyl - 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuran]ethylamine hydrochloride, M.P. 163—164°; yield 2.97 g, 74% of theoretical value. In a similar manner are obtained from 3.40 g of 2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranacetic acid pyrrolidide, M.P. 101—102°, after reduction with 10 g of lithium aluminium chloride—,from acetone/ether—2.7 g of 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 191—192°; yield 75% of theoretical value.

In an analogous manner is obtained from 3.85 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranacetic acid and 6.1 ml of thionyl chloride, the acid chloride and from the latter, after treatment with 12.3 ml of pyrrolidine—after final processing and crystallisation from chloroform/petroleum ether—3.65 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranacetic acid pyrrolidide, M.P. 128—129° (yield 81% of theoretical value). In like manner is obtained, after reaction of the acid chloride with diethylamine, the oily 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranacetic acid diethylamide; yield 4.2 g (93% of theoretical value). IR in CH_2Cl_2 = 1640 cm^{-1} CO. Furthermore, analogously to example 27, are obtained from 3.85 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranacetic acid pyrrolidide, after reduction with 5.0 g of lithium aluminium hydride and conversion of the crude base into the hydrochloride after crystallisation from acetone/water, 3.22 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 196—197°; yield 79% of theoretical value.

In the same manner is obtained from 2.1 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranacetic acid diethylamide, after reduction with 3.0 g of lithium aluminium hydride and conversion of the crude base into the hydrochloride—after crystallisation from acetone/ether—1.41 g of 2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - [2 - diethylamino) - ethyl] - benzofuran hydrochloride, M.P. 129—130°; yield 64% of theoretical value.

In an analogous manner is obtained from 0.34 g of 2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuranacetic acid and 0.5 ml of thionyl chloride, the acid chloride and from the latter, after treatment with 1.0 ml of diethyl amine and after processing, are obtained 0.36 g of 2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuranacetic acid diethylamide as colourless oil; yield 91% of theoretical value. IR in CH_2Cl_2 = 1640 cm^{-1} CO. Moreover there are obtained from 0.35 g of 2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3-benzofuranacetic acid diethylamide, after reduction with 0.8 g of lithium aluminium hydride and conversion of the crude base into the hydrochloride, after crystallisation from acetone/ether, 0.26 g of 2 - (*p* - ethoxybenzyl) - 3 - [2 - diethylamino) - ethyl] - 5 - methoxybenzofuran hydrochloride, M.P. 123—124°; yield 70% of theoretical value.

Example 30

a) 2.5 g of 1 - (*p* - ethoxyphenyl) - 6 - methyl - 3,4 - dihydrobenzofuro[2,3c]pyridine are heated under nitrogen with 10 ml of hydrazine hydrate in 30 ml of diethylene glycol for 10 minutes to 200°, then cooled and 5.5 g of potassium hydroxide are added. The reaction mixture is subsequently heated for 2 hours to 200° and, with initial foaming, water vapour and nitrogen escape during this period. After allowing the reaction mixture to cool, it is poured into water and the base extracted with ether. The ether solution, washed with water and dried over sodium sulphate yields, after concentrating by evaporation, 2.3 g of colourless oil which, after a short time, solidifies to give fibrous crystals of the 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran]ethylamine, M.P. 49—50°; yield 91% of theoretical value. By adding hydrogen chloride gas in ether, the hydrochloride is obtained which, after recrystallisation from methanol/ether, melts at 176—177°.

b) To a solution of 0.30 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran]-ethylamine in 5 ml of acetonitrile are added 0.20 g of diisopropylamine and 0.34 g of 1,5-dibromopentane. Refluxing is carried out for 24 hours, the acetonitrile removed by concentrating by evaporation *in vacuo* and the residue taken up with dilute soda solution and ether. The ether extract is extracted with dilute hydrochloric acid, the acid extracts are made alkaline soda solution and the thereby oily precipitated base is extracted with ether. The ethereal extract, washed with water, is dried over sodium sulphate and concentrated by evaporation *in vacuo*. The residual crude 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine is dissolved in ether and a small excess of ethereal hydrochloric acid is added. From the precipitated hydrochloride are obtained, after recrystallisation from acetone, 0.20 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 192—193°; yield 48% of theoretical value.

In an analogous manner there are obtained from 0.30 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran]ethylamine and 0.32 g of 1,4 - dibromobutane, after crystallisation from acetone/ether, 0.21 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl -

3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 167—169°; yield 52% of theoretical value.

Furthermore, from 0.3 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine and 0.36 g of propylbromide are obtained, after crystallisation from acetone/ether, 0.18 g of N,N - dipropyl - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine hydrochloride, M.P. 106—107°; yield 42% of theoretical value; and from 0.30 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran]ethylamine and 0.32 g of ethyl bromide are obtained, after crystallisation from acetone/ether, 0.24 g of N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran]ethylamine hydrochloride, M.P. 139—140°; yield 60% of theoretical value.

EXAMPLE 31

1.0 g of *p* - toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl ester is heated in a pressure vessel with 4.0 g of liquid ammonia for 6 hours to 110°. After cooling to room temperature, the ammonia is allowed to escape and the residue taken up in water and ether. The ether extract is washed with water and extracted with dilute hydrochloric acid. The acid extracts are adjusted to pH 9 with concentrated ammonia solution and the precipitated base is extracted with ether. The ether extract yields, after washing, drying over sodium sulphate and concentrating by evaporation, 0.7 g of oily 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran]ethylamine. By adding hydrogen chloride gas in ether is obtained the hydrochloride which, after recrystallisation from acetone/ether, melts at 216—219°; yield 75% of theoretical value.

From 0.33 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran]ethylamine and 0.33 g of ethyl bromide are obtained, after crystallisation from acetone/ether, 0.25 g of N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran]ethylamine hydrochloride, M.P. 129—130°; yield 59% of theoretical value.

In an analogous manner are obtained from 0.33 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran]ethylamine and 0.34 g of 1,5 - dibromopentane, after crystallisation from dioxane/water, 0.19 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 212—213°; yield 44% of theoretical value. Furthermore, from 0.33 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran]ethylamine and 0.32 g of 1,4-dibromobutane are obtained, after crystallisation from acetone/water, 0.22 g of 1 - [2 - [2 - (p - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 196—197°; yield 53% of theoretical value.

EXAMPLE 32

From 2.4 g of *p* - toluenesulphonic acid 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester are obtained, after reaction with 10.0 g of ammonia, 1.17 g of 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine as colourless oil (yield 72% of theoretical value). From 0.31 g of this oil and 0.34 g of 1,5-dibromopentane are obtained, after conversion into the hydrogen sulphate and crystallisation from acetone, 0.25 g of 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrogen sulphate, M.P. 171—172°; yield 50% of theoretical value.

In an analogous manner from 0.31 g of 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuran]ethylamine and 0.32 g of 1,4-dibromobutane are obtained, after crystallisation from acetone/ether, 0.22 g of 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 191—192°; yield 53% of theoretical value.

In the same manner are obtained with 0.36 g of propyl bromide, 0.20 g of N,N - dipropyl - 2 - [2 - (*p* 1 isopropoxybenzyl) - 5 - methyl - 3 - benzofuran]ethylamine hydrochloride, M.P. 163—164°; and from 2.4 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 5 - methoxy - 5 - benzofuranyl] - ethyl ester are obtained, after reaction with 10.0 g of ammonia, 1.2 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuran]ethylamine as oil; yield 74% of theoretical value (IR in Nujol* = 3380 cm^{-1} NH_2). 1.2 g of this oil are reacted with 1.30 g of ethyl bromide and, after crystallisation from acetone/ether, 0.95 g of 2 - (*p* - ethoxybenzyl)-5 - methoxy - 3 - [2 - (diethylamino) - ethyl]-3 - benzofuran hydrochloride are produced; yield 62% of theoretical value, M.P. 123—124°.

EXAMPLE 33

a) To 4.2 g of 2 - [5 - methyl - 3 - benzofuran]ethanol are added 20 ml of pyridine and 5 ml of acetic anhydride. After standing for 20 hours at room temperature, the solution is poured into water and stirred. After half an hour, the precipitated oil is separated by decanting and is taken up in ether. The ether solution is washed with dilute hydrochloric acid, water and sodium bicarbonate solution, dried over sodium sulphate and concentrated by evaporation. 4.9 g of crude 2 - (5 - methyl - 3 - benzofuranethyl)acetic acid ester are obtained as yellowish oil; yield 89% of theoretical value.

b) 4.9 g of crude 2 - (5 - methyl - 3 - benzofuran)ethylacetic acid ester and 4.4 g of *p*-ethoxybenzoyl chloride are dissolved in 25 ml of carbon disulphide and, after cooling

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the solution to 0°, 6.5 g of tin tetrachloride are added dropwise, while stirring and in the course of half an hour. The solution thereby turns brown and a precipitate is formed. The mixture is stirred for a further 6 hours at room temperature. After decomposing with water, the reaction vessel is rinsed with 100 ml of chloroform into a separating funnel. The yellowish organic phase is washed with water, dried over sodium sulphate and concentrated by evaporation. Crystallisation of the residue from methanol yields 5.5 g of 2 - [5 - methyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran]ethylacetic acid ester, M.P. 94—95°; yield 67% of theoretical value.

c) 5.3 g of 2 - [5 - methyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran]ethylacetic acid ester are refluxed to boiling with 0.8 g of sodium hydroxide in 30 ml of 70% ethanol for 2 hours in the reflux condenser. Water is gradually added to the hot solution, whereupon crystallisation occurs. After recrystallisation from methanol/water are obtained 4.3 g of 2 - [5 - methyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran]ethanol, M.P. 128—130°; yield 95% of theoretical value.

d) 4.3 g of 2 - [5 - methyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran]ethanol are dissolved in 45 ml of absolute pyridine and, after cooling the solution to −15°, 7.0 g of *p*-toluenesulphochloride are added in portions. After standing for 18 hours at 0°, the solution is poured into ice-water, the precipitated oil separated and triturated. Crystallisation occurs after some time. Recrystallisation from chloroform/ether yields 5.4 g of 2 - [5 - methyl - 2 - (*p* - ethoxybenzoyl - 3 - benzofuran]-ethyl *p* - toluenesulphonic acid ester, M.P. 125—126°; yield 65% of theoretical value.

e) 2.5 g of the *p*-toluenesulphonic acid ester from d) are refluxed to boiling with 25 ml of pyrrolidine for 5 hours in the reflux condenser. The solution is then concentrated by evaporation *in vacuo* and the residue crystallised from water. After recrystallisation from methanol/acetone, 2.0 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 202—205° (decomposition) are obtained; yield 90% of theoretical value.

f) 2.5 g of the *p*-toluenesulphonic acid ester from d) are refluxed in a reflux condenser with 25 ml of piperidine for 5 hours. The solution is concentrated by evaporation *in vacuo*, 20 ml of benzene are added and again concentrated by evaporation. The residue is taken up in water and ether. The ethereal phase is repeatedly washed with water and then extracted 3 times using 5 ml of 1N hydrochloric acid each time. The acid extracts are adjusted to pH 9 with concentrated ammonia and the thereby obtained oily precipitated base is extracted by shaking with ether. The ethereal extract, washed with water, is dried over sodium sulphate and concentrated by evaporation in vacuo. The oily residue is dissolved in ether and some acetone and a small excess of dilute ethereal sulphuric acid is added. The precipitated oil crystallises upon triturating. After recrystallisation from methanol/acetone are obtained 2.1 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrogen sulphate, M.P. 150—151°; yield 80% of theoretical value.

g) 0.7 g of the *p*-toluenesulphonic acid ester from d) are refluxed with 20 ml of diethylamine for 48 hours. The procedure was otherwise analogous to that described in f) and 0.4 g of N - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - diethylamine hydrogen sulphate, M.P. 195—197°, are obtained; yield 56% of theoretical value.

h) Analogously to f), 6.0 g of the *p*-toluenesulphonic acid ester from d) are reacted with 60 ml of di - n - butylamine. The obtained crude base is converted, analogously to e), into the hydrochloride. After crystallisation from acetone, 4.6 g of N - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - di - n - butylamine hydrochloride, M.P. 188—190°, (yield 77% of theoretical value) are obtained.

i) 0.75 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride are converted, by shaking with 2N soda solution, into the base and the latter is isolated by extraction with ether, washing of the ethereal phase with water, drying over sodium sulphate and concentrating by evaporation.

To the oily base are added 7 ml of a 0.7-molar solution of diborane in tetrahydrofuran and the mixture maintained for 20 hours at room temperature. The solution is then decomposed by addition of methanol, made acid with ethereal hydrochloric acid and refluxed for one hour to boiling in the reflux condenser. The solution is then concentrated by evaporation *in vacuo*, methanol is added and again the solution is concentrated by evaporation. The residue is taken up in water, the obtained cloudy solution made strongly alkaline with concentrated ammonia and extracted with ether. The ether phase is repeatedly washed with water, dried over sodium sulphate and concentrated by evaporation. The residue is taken up with methanol, a small excess of methanolic hydrochloric acid is added and the solution boiled up with some animal charcoal. It is then filtered and the filtrate concentrated by evaporation *in vacuo*. The evaporation residue crystallises upon triturating with acetone. After recrystallising from methanol/acetone, 0.58 g of 1 - [2 - [2 - *p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 167—169°, are obtained; yield 84% of theoretical value.

j) Analogously to i), from 2.0 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 -

benzofuranyl] - ethyl] - piperidine hydrogen sulphate are obtained, after conversion into the base and reduction of the latter with 20 ml of a 0.7-molar solution of diborane in tetrahydrofuran, 1.34 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 192—193°; yield 79% of theoretical value.

k) Analogously to i), from 2.0 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - diethylamine hydrogen sulphate are produced, after conversion into the base and reduction of the latter with 20 ml of a 0.7-molar solution of diborane in tetrahydrofuran, 1.23 g of N - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - diethylamine hydrochloride, M.P. 139—140°; yield 72% of theoretical value.

EXAMPLE 34

1.0 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3- benzofuranyl] - ethyl] - pyrrolidine - hydrochloride is dissolved in 20 ml of diethylene glycol, treated with 4.5 ml of hydrazine hydrate and heated under an atmosphere of nitrogen in a distillation apparatus until the temperature of the reaction mixture reaches 195°. The temperature is kept at 195° for 10 minutes, then allowed to cool to 150°, and 2.2 g of potassium hydroxide are added. The generation of nitrogen which commences is brought to completion by heating for 2 hours at 200°. The reaction mixture is then cooled, poured into water and extracted with ether. The ether extract is washed several times with water, dried over sodium sulphate, and concentrated by evaporation. The residue is taken up with ether and a small amount of acetone, and a slight excess of ethereal hydrochloric acid is added. Upon trituration, 0.7 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride having a melting point of 167—169°, crystallize. Yield: 81% of theory.

In an analogous manner, the following are obtained: from 2.0 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrogen sulphate, by treating with 8 ml of hydrazine hydrate in 40 ml of diethylene glycol and 4.4 g of potassium hydroxide,

1.35 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] piperidine hydrochloride, M.P. 192—193°. Yield: 80% of theory;

from 1.1 g of N - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - diethylamine hydrogen sulphate, 0.71 g of N - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - diethylamine hydrochloride, m.p. 139—140°. Yield: 75% of theory; and

from 4.5 g of N - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - di - n - butylamine hydrochloride, 2.0 g of N - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - di - n - butylamine hydrochloride, m.p. 106—107°. Yield: 45% of theory.

EXAMPLE 35

a) Analogously to Example 33 b), 12.2 g of crude 2 - (5 - methyl - 3 - benzofuran) ethyl acetate are reacted with 12.5 g of *p*-butoxybenzoyl chloride and 16.1 g of tin tetrachloride in 60 ml of carbon disulphide. Crystallisation of the crude product from methanol yields 17.0 g of 5 - methyl - 2 - (*p* - butoxybenzoyl) - 3 - benzofuran - acetic acid ester M.P. 76—77°. Yield 78% of theory.

b) Analogously to Example 33 c), 17.0 g of the ester obtained in a) are hydrolysed with 2.4 g of sodium hydroxide in 140 ml of 70% ethanol. Upon the addition of water, the product crystallises. Recrystallisation from methanol yields 14.0 g of 2 - [5 - methyl - 2 - (*p* - butoxy - benzoyl) - 3 - benzofuran] - ethanol, m.p. 121—122°. Yield 92% of theory.

c) Analogously to Example 33 d), 14.0 g of 2 - [5 - methyl - 2 - (*p* - butoxybenzoyl) - 3 - benzofuran] - ethanol in 125 ml of absolute pyridine are reacted with 25 g of *p* - toluene - sulphochloride. After crystallisation from ether/petroleum ether, 17.5 g of *p* - toluene - sulphonic acid 2 - [5 - methyl - 2 - (*p* - butoxybenzoyl) - 3 - benzofuran]ethyl ester, M.P. 100—101°, are obtained, yield 87% of theory.

d) Analogously to Example 33 e), 9.0 g of *p* - toluene - sulphonic acid 2 - [5 - methyl - 2 - (*p* - butoxybenzyl) - 3 - benzofuran] ethyl ester are treated with 40 ml of pyrrolidine. Crystallisation from water/acetone yields 6.2 g of 1 - [2 - [2 - (*p* - butoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, m.p. 216—218°.

e) Analogously to Example 33 i), from 1.0 g of 1 - [2 - [2 - (*p* - butoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, there is obtained 0.58 g of 1 - [2 - [2 - (*p* - butoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, m.p. 164—166°. Yield: 60% of theory.

EXAMPLE 36

6 - methyl - 3 - benzofuran - acetic acid is produced according to the article by B. B. Dey and K. Radhabai, J. ind. chem. Soc., *11*, 635 (1934).

22.0 g of 6 - methyl - 3 - benzofuran - acetic acid are reduced analogously to Example 1 c) with 12 g of lithium aluminium hydride. 18.0 g of 2 - (6 - methyl - 3 - benzofuran)-ethanol are obtained as a colourless oil. Yield 96% of theory.

Analogously to example 33 a), 18.5 g of 2 - (6 - methyl - 3 - benzofuran) - ethanol are esterified with 25 ml of acetic anhydride in 90 ml of pyridine. 20 g of crude acetic acid 2 - (6 - methyl - 3 - benzofuranyl)ethyl ester are obtained as a colourless oil. Yield 88% of theory.

Analogously to Example 33 b), 19.5 g of acetic acid 2 - (6 - methyl - 3 - benzofuranyl)-ethyl ester are reacted with 17.6 g of *p* - ethoxybenzoyl chloride and 26 g of tin tetrachloride. After crystallization from methanol, 28.0 g of acetic acid 2 - [6 - methyl - 2 - (p - ethoxybenzoyl) - 3 - benzofuranyl]-ethyl ester, m.p. 91—92°, are obtained. Yield 85% of theory.

Analogously to Example 33 c), 28.0 g of the ester obtained in the previous step are hydrolysed with 4.2g of sodium hydroxide in 155 ml of 70% ethanol. After the addition of water, the product precipitates as crystals. Recrystallization from methanol yields 23.8 g of 2 - [6 - methyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran] - ethanol, m.p. 105—106°. Yield: 96% of theory.

Analogously to Example 33 d), 23.5 g of ethanol obtained in the previous step are reacted with 6 g of *p* - toluenesulphochloride in 224 ml of absolute pyridine. Crystallization from ether/petroleum ether yields 28.5 g of p - toluenesulphonic acid 2 - [6 - methyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran] ethyl ester, m.p. 97—98°. Yield: 82% of theory.

Analogously to Example 33 f), 6.0 g of *p* - toluene - sulphonic acid ester obtained in the previous step are reacted with 60 ml of pyrrolidine. The crude base obtained is converted, analogously to Example 33 e), to the hydrochloride. After crystallization from acetone/ether, 4.4 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 6 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, m.p. 203—204°, are obtained. Yield: 86% of theory.

Analogously to Example 33 i), from 4.3 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 6 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, there are obtained 3.1 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 6 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, m.p. 179—180°. Yield 75% of theory.

EXAMPLE 37

a) 10.0 g of 3 - ethyl - phenol are introduced into a mixture of 20.0 g of acetone dicarboxylic acid and 30 ml of concentrated sulphuric acid which has been cooled to 0°. After addition of a further 10 ml of concentrated sulphuric acid, the reaction mixture is kept for 18 hours at 0° and then poured into 500 ml of ice-water. The precipitate obtained is removed by filtration and then extracted a number of times with cold, saturated sodium bicarbonate solution. From the extracts, which have been clarified by filtration and acidified with concentrated hydrochloric acid to a pH of 1, a crystalline precipitate is obtained. Recrystallization from ethanol water yields 5.0 g of 7 - ethyl - 4 - coumarin - acetic acid, M.P. 187—188°. Yield: 26% of theory.

b) 20.0 g of 7 - ethyl - 4 - coumarin - acetic acid are suspended in 90 ml of glacial acetic acid and treated all at once with a solution of 18 g of bromine in 90 ml of glacial acetic acid. After heating for a short time on a boiling water bath, a yellow solution is obtained, which, upon cooling, yields crystalline 7 - ethyl - 4 - coumarin - 1′ - bromoacetic acid. The crystals are removed by filtration and extracted a number of times with cold sodium bicarbonate solution. The extracts are adjusted to a pH of 1 with concentrated hydrochloric acid, whereby the product precipitates as crystals. Removal by filtration and crystallisation from ethanol yields 20.0 g of 7 - ethyl - 4 - coumarin - 1′ - bromoacetic acid, m.p. 162—164°. Yield: 75% of theory.

c) 20.0 g of 7 - ethyl - 4 - coumarin - 1′ - bromoacetic acid are suspended in 100 ml of xylene and the mixture is heated for 24 hours to boiling under a reflux condenser. The acid dissolves and carbon dioxide escapes. The reaction mixture is then cooled, whereby crude 7 - ethyl - 4 - bromomethyl - coumarin crystallizes. After recrystallization from alcohol, 14.0 g of the coumarin, having a melting point of 157—158°, are obtained. Yield: 82% of theory.

d) 14.0 g of 7 - ethyl - 4 - bromomethyl-coumarin are treated with 100 ml of 30% potassium hydroxide solution and the mixture is heated to boiling. As soon as a clear solution is obtained, it is cooled and, with the addition of ice, is adjusted to a pH of 1 with concentrated hydrochloric acid. The precipitate is removed by filtration and then extracted a number of times with sodium bicarbonate solution. The extracts are adjusted to a pH of 1 with concentrated hydrochloric acid, and the crystalline precipitate obtained is removed by filtration. Crystallisation of the product from ether/petroleum ether yields 4.3 g of 6 - ethyl - 3 - benzofuran - acetic acid, m.p. 75—76°. Yield: 40% of theory.

e) 4.3 g of 6 - ethyl - 3 - benzofuranacetic acid are reduced with 2.5 g of lithium aluminium hydride in 70 ml of ether. 4.0 g of 2 - (6 - ethyl - 3 - benzofuran)ethanol are obtained as a colourless oil; yield quantitative.

f) From 4.0 g of 2 - (6 - ethyl - 3 - benzofuran)ethanol are obtained, analogously to example 33a), 4.2 g of acetic acid 2 - (6 - ethyl - 3 - benzofuran)ethyl ester as a colourless oil; yield 86% of theoretical value.

g) Analogously to example 33 b), 4.2 g of acetic acid 2 - (p - ethyl - 3 - benzofuran) ethyl ester are treated with 3.5 g of *p*-ethoxybenzoyl chloride and 5.0 g of tin tetrachloride. By this means are obtained 6.2 g of oily acetic

acid 2 - [6 - ethyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran]ethyl ester; yield 90% of theoretical value.

h) From 6.2 g of acetic acid ester obtained in the previous step are obtained, analogously to example 33c), 4.5 g of crude oily 2 - [6 - ethyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran]ethanol; yield 82% of theoretical value.

i) From 4.5 g of crude 2 - [6 - ethyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran]ethanol are obtained, analogously to example 33 d) and after crystallisation from ether, 3.0 g of *p*-toluenesulphonic acid 2 - [6 - ethyl - 2 - (*p* - ethoxybenzoyl) - 3 - benzofuran]ethyl ester, M.P. 86—87°; yield 46% of theoretical value.

j) From 2.7 g of the *p*-toluenesulphonic acid ester obtained in the previous step is obtained, analogously to example 33 f), by reaction with 27 ml of pyrrolidine and conversion of the obtained crude base into the hydrochloride and after recrystallisation from acetone, 1.0 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 6 - ethyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 192—193°; yield 43% of theoretical value.

k) From 1.0 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 6 - ethyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride are obtained, analogously to example 34), 0.6 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 6 - ethyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 163—164°; yield 62% of theoretical value.

From 6.0 g of *p*-toluenesulphonic acid 2 - [6 - methyl - 2 - (*p* - ethoxybenzoyl) - 3-benzofuran]ethyl ester (obtained analogously to a)—i)) and 60 ml of diethylamine is obtained the crude base and this is converted into the hydrochloride. After crystallisation from acetone there are obtained 3.7 g of N - [2 - [2 - (*p* - ethoxybenzoyl) - 6 - methyl-3 - benzofuranyl] - ethyl] - diethylamine hydrochloride, M.P. 185—187°; yield 69% of theoretical value.

From 3.7 g of N - [2 - [2 - (*p* - ethoxybenzoyl) - 6 - methyl - 3 - benzofuranyl] - ethyl] - diethylamine hydrochloride are obtained, by reduction with diborane and after crystallisation from acetone/ether, 2.0 g of N - [2 - [2 - (*p* - ethoxybenzyl) - 6 - methyl-3 - benzofuranyl] - ethyl] - diethylamine hydrochloride, M.P. 135—137°; yield 56% of theoretical value.

Example 38

90 g of 5 - chloro - 3(2H) - benzofuranone are added to a solution of 90 g of cyanoacetic acid ethyl ester in 150 ml of toluene and 3 ml of pyrrolidine are added. After the exothermic reaction has ceased, the mixture is refluxed for 24 hours, whereby the azeotropically distilled water, formed during condensation, is removed by means of a water-separating agent. After the reaction is finished, the toluene and the excess cyanoacetic acid ethyl ester are distilled off *in vacuo*. The darkly coloured distillation residue is refluxed with a solution of 80 g of sodium hydroxide in 800 ml of 90% ethanol for 48 hours. Initially, crystals of 5 - chloro - 3 - benzofuranacetamide hereby precipitate, which for the most part gradually go into solution again. Finally, the ethanol is removed *in vacuo* and the mixture remaining is extracted with water. The filtered alkaline extracts are adjusted to pH 1 with concentrated hydrochloric acid, while cooling with ice, and extracted with ether. The ethereal extracts are washed with water, dried over sodium sulphate and concentrated by evaporation. The obtained crude 5 - chloro - 3 - benzofuranacetic acid yields, after twice crystallising from methanol/water, 31.5 g of crystals, M.P. 140—141° (in a sealed tube); yield 28% of theoretical value.

4.2 g of 5 - chloro - 3 - benzofuranacetic acid are reduced with 3.0 g of lithium aluminium hydride. 3.15 g of 2 - (5 - chloro - 3 - benzofuran)ethanol are obtained as an oil; yield 80% of theoretical value. IR in CH_2Cl_2 = 3590 cm^{-1} OH.

11.2 g of 2 - (5 - chloro - 3 - benzofuran)-ethanol are acetylated with 13.6 ml of acetic anhydride and 13.0 g of acetic acid 2 - (5 - chloro - 3 - benzofuranyl) - ethyl ester are obtained as an oil; yeld 95% of theoretical value, (IR in CH_2Cl_2 = 1730 cm^{-1} CO).

6.5 g of the acetic acid ester are reacted with 7.2 g of *p*-ethoxybenzoyl chloride and 8.0 g of tin tetrachloride. The obtained oil yields, from methanol, 3.2 g of acetic acid 2 - [2 - (*p* - ethoxybenzoyl) - 5 - chloro - 3 - benzofuranyl] - ethyl ester, M.P. 118—119°; yield 29% of theoretical value.

3.2 g of acetic acid 2 - [2 - (*p* - ethoxybenzoyl) - 5 - chloro - 3 - benzofuranyl] - ethyl ester are hydrolysed with 0.7 g of sodium hydroxide in 35 ml of 85% ethanol. The crystals obtained upon cooling are filtered off and recrystallised from alcohol/water. 1.7 g of 2 - [2 - (*p* - ethoxybenzoyl) - 5 - chloro - 3 - benzofuran]ethanol, M.P. 120—121°, are obtained; yield 60% of theoretical value.

From 1.2 g of this alcohol are obtained, after reaction with 2.0 g of *p*-toluenesulphochloride and crystallisation from ether, 1.7 g of *p* - toluenesulphonic acid 2 - [2 - (*p*-ethoxybenzoyl) - 5 - chloro - 3 - benzofuranyl] - ethyl ester, M.P. 128—129°; yield 97% of theoretical value.

1.7 g of this *p*-toluenesulphonic acid ester are reacted with 10 ml of pyrrolidine. After conversion of the isolated crude base into the hydrochloride and crystallisation from methanol/water, 1.2 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 188—190°, are obtained; yield 88% of theoretical value.

Analogously to example 34), 1.2 g of 1 - [2 - [2 - (*p* - ethoxybenzoyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride are converted into the free base and the latter is reduced with 4.5 ml of hydrazine hydrate. After crystallisation from acetone/water there is obtained 1.0 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 196—197°; yield 86% of theoretical value.

EXAMPLE 39

a) 63.5 g of acetic acid 2 - (5 - methyl - 3 - benzofuranyl) - ethyl ester are reacted with 61 g of *p*-isopropoxybenzoyl chloride and 84 g of tin tetrachloride. After crystallisation from methanol are obtained 76 g of acetic acid 2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester, M.P. 81—82°; yield 70% of theoretical value.

b) 76 g of this acetic acid ester, dissolved with 11 g of sodium hydroxide, are hydrolysed in 270 ml of 50% ethanol. After cooling of the reaction mixture and addition of water, 66 g of crystallised 2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuran]ethanol, M.P. 114—115°, are obtained; yield 97% of theoretical value.

c 66 g of 2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuran]ethanol are reacted with 122 g of *p*-toluenesulphochloride. After crystallisation from ether are obtained 79 g of *p* - toluenesulphonic acid 2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester, M.P. 93—94°; yield 82% of theoretical value.

From 6.0 g of this *p*-toluenesulphonic acid ester and 30 ml of morpholine is obtained the 4 - [2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - morpholine. The hydrochloride of the latter melts, after recrystallisation from acetone/ether, at 220—222°; yield 5.0 g, 92% of theoretical value.

d) From 9.0 g of the *p*-toluenesulphonic acid ester obtained in c) and 45 ml of pyrrolidine is obtained the 1 - [2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine, the hydrochloride of which melts, after recrystallisation from acetone/ether, at 192—194°; yield 7.5 g, 96% of theoretical value.

From 5.0 g of the *p*-toluenesulphonic acid ester obtained in c) and 25 ml of piperidine is obtained the 1 - [2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine. The hydrochloride of the latter melts, after recrystallisation from acetone/ether, at 207—208°; yield 3.88 g, 90% of theoretical value.

e) Analogously to example 34) are obtained from 5.0 g of 4 - [2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - morpholine, after conversion into the free base and reduction of the latter with 20 ml of hydrazine hydrate, the 4 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - morpholine. The hydrochloride of the latter melts, after recrystallisation from acetone/ether, at 199—200°; yield 3.6 g, 68% of theoretical value.

In an analogous manner are obtained from 7.0 g of 1 - [2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine, after reduction with 29 ml of hydrazine hydrate, the 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine. The hydrochloride of the latter melts, after recrystallisation from acetone/ether, at 191—192°; yield 4.8 g, 65% of theoretical value.

From 2.2 g of 1 - [2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine is obtained the 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine. The hydrogen sulphate of the latter melts, after recrystallisation from acetone, at 171—172°; yield 1.9 g, 83% of theoretical value.

From 2.5 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethyl ester and 25 ml of di - n - propylamine are obtained after crystallisation from acetone/ether, 1.1 g of N,N - dipropyl - 2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethylamine hydrochloride, M.P. 198—199°; yield 45% of theoretical value.

f) 1.0 g of N,N - dipropyl - 2 - [2 - (*p* - isopropoxybenzoyl) - 5 - methyl - 3 - benzofuranyl] - ethylamine hydrochloride is treated with 4.5 ml of hydrazine hydrate in 20 ml of diethylene glycol and 2.2 g of potassium hydroxide. After crystallisation from acetone are obtained 3.78 g of N,N - dipropyl - 2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethylamine hydrochloride, M.P. 163—164°; yield 80% of theoretical value.

EXAMPLE 40

a) 3.6 g of 2 - (*p* - ethoxybenzyl) - 2,3 - dihydro - 3 - hydroxy - 5 - methyl - 3 - benzofuranacetic acid methyl ester (mixture of the isomeric hydroxy esters) are added to a suspension of 1.5 g of lithium aluminium hydride in 30 ml of tetrahydrofuran. The mixture is refluxed while stirring, for 3 hours. It is then allowed to cool and 60 ml of ether are added. The mixture is decomposed by slowly adding dropwise 1.75 ml of water, 1.25 ml of concentrated sodium hydroxide solution and 5.25 ml of water. After decanting the precipitate, washing it with ether and concentrating the organic solutions by evaporation, an oily product is obtained, which is taken up in ether. The ethereal solution is washed with water, dried over sodium sulphate and concentrated by evaporation *in vacuo*. The oil remaining yields, from ether/petroleum ether, 1.3 g of 2 - [2 - (*p* - ethoxybenzyl) - 2,3 -

dihydro - 3 - hydroxy - 5 - methyl - 3 - benzofuran]ethanol, M.P. 98—99°; yield 39% of theoretical value.

b) 0.7 g of the alcohol, obtained according to a), are reacted with 1.5 g of *p*-toluenesulphochloride in 8 ml of absolute pyridine. After completion of the reaction, the mixture is poured into ice-water and the precipitated oil taken up in ether. The ethereal solution is separated, by washing with 0.2N sulphuric acid, from adhering pyridine. It is then washed with water, dried over sodium sulphate and concentrated by evaporation *in vacuo* at 20°. The obtained oil yields, from ether/petroleum ether, 0.95 g of *p*-toluenesulphonic acid 2 - [2 - (*p* - ethoxybenzyl) - 2,3 - dihydro - 3 - hydroxy - 5 - methyl - 3 - benzofuranyl] - ethyl ester, M.P. 74—75° (decomposition); yield 87% of theoretical value.

c) 0.20 g of the *p*-toluenesulphonic acid ester, obtained according to b), are reacted with 1 ml of pyrrolidine or piperidine. After recrystallisation from acetone/ether are obtained 0.12 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride (yield 69% of theoretical value), M.P. 167—169°, or 0.11 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 192—193° (yield 61% of theoretical value).

In an analogous manner, 0.2 g of the *p*-toluenesulphonic acid ester, obtained according to b), are reacted with 1 ml of di-n-propylamine. After crystallisation from acetone/ether, 0.1 g of N,N - dipropyl - 2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranethylamine hydrochloride, M.P. 107—108°, is obtained; yield 54% of theoretical value.

Example 41

a) 0.6 g of 2 - [5 - methyl - 2 - (*p* - ethoxybenzyl) - 3 - benzofuran]ethanol are dissolved in 1.0 ml of absolute pyridine. The solution is cooled to −15° and 0.15 ml of thionyl bromide are added. The formation of a precipitate and a temperature increase to −2° are thereby observed. After maintaining the solution at 0° for 48 hours, water is added, the precipitated oil taken up in ether and washed with 1N hydrochloric acid and water. The ethereal phase is dried over sodium sulphate and concentrated by evaporation. By this means 0.7 g of crude 2 - [5 - methyl - 2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl] - ethyl bromide remain as yellowish oil. The latter is heated with 0.5 ml of pyridine for 3 hours to 90° and the excess pyridine subsequently distilled off in vacuo. The residue is taken up in chloroform and is separated from adhering pyridine by being shaken with a little 2N sulphuric acid. The chloroform phase is dried over Na_2SO_4 and concentrated by evaporation. The obtained oil, after crystallisation from acetone/ether, yields 0.15 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyridinium hydrogen sulphate, M.P. 193—194°; yield 17% of theoretical value.

b) 0.04 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyridinium hydrogen sulphate are dissolved in 10 ml of methanol. Some drops of glacial acetic acid are added and the solution is hydrogenated over 0.02 g of platinum catalyst. After the hydrogen absorption has finished, the catalyst is filtered off and the solution concentrated by evaporation *in vacuo*. The residue is taken up in water, made alkaline with several drops of concentrated ammonia and extracted with ether. The ethereal phase is washed with water, dried over sodium sulphate and concentrated by evaporation *in vacuo*. The obtained base is taken up in ether and ethereal hydrochloric acid is added. Upon triturating are obtained 0.02 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride, M.P. 192—193°.

The following piperidines are produced in an analogous manner from corresponding pyridinium compounds:

1 - [2 - [2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl] - ethyl] - piperidine, the hydrochloride melts at 194—196° (from acetone/ether),

1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - piperidine, the hydrochloride melts, after recrystallisation from dioxane/water, at 212—213° and

1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine, the hydrochloride melts at 171—172°, after recrystallisation from acetone.

Example 42

a) 1.0 g of 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran]ethylamine is dissolved in 20 ml of ether and to the solution are added 2 ml of acetic anhydride. The solution is allowed to stand for 20 hours at room temperature, whereupon 5 ml of chloroform are added and the reaction solution is repeatedly extracted with dilute hydrochloric acid. It is then washed with water, dried over sodium sulphate and concentrated in vacuo by evaporation. From the oil which remains are produced upon crystallisation from ether, 1.05 g of N - [2 - [2 - (*p* - ethoxybenzyl) 5 - methyl - 3 - benzofuran]ethylacetamide, M.P. 114—115°; yield 90% of theoretical value.

b) 1.0 g of N - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran]ethyl] - acetamide is slowly added in portions to a solution of 1.0 g of lithium aluminium hydride in 60 ml of ether. After being stirred and refluxed for 20 hours, the reaction mixture is cooled to 0° and decomposed by the suc-

cessive addition of 1.1 ml of water, 0.8 ml of concentrated sodium hydroxide solution and 3.4 ml of water. The ether solution is decanted off from the precipitate and the latter subsequently washed with ether. After concentrating the ethereal solution by evaporation, the crude N - ethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine is obtained as colourless oil. With ethereal hydrochloric acid, this yields the hydrochloride which, after recrystallisation from acetone/ether, melts at 153—154°; yield 0.7 g, 73% of theoretical value.

c) 0.33 g of N - ethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine are dissolved in 30 ml of absolute ethanol and hydrogenated with addition of 2.5 ml of acetaldehyde in the presence of 0.5 g of Raney-nickel. After the hydrogen absorption is finished, the catalyst is separated by filtration, the filtrate concentrated by evaporation and the residue taken up in ether. The ethereal solution is extracted with dilute hydrochloric acid, the acid extracts are rendered basic with ammonia and the oily precipitated base is extracted with ether. The ethereal solution is washed with water and dried over sodium sulphate and then concentrated by evaporation. The residual crude base is taken up in acetone and ethereal hydrochloric acid is added until an acid reaction is obtained. 0.1 g of animal charcoal is added to the solution, the latter is boiled, filtered through kieselguhr and the filtrate is concentrated by evaporation *in vacuo*. After crystallisation from acetone/ether, the residue yields 0.12 g of N,N - diethyl 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] ethylamine hydrochloride, M.P. 139—140°; yield 30% of theoretical value.

0.35 g of N - propyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] ethylamine are hydrogenated in an analogous manner in the presence of 3.0 g of propionic aldehyde and 0.5 g of Raney-nickel. After purification with animal charcoal is obtained, from acetone/ether, 0.10 g of N,N - dipropyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] ethylamine hydrochloride, M.P. 106—107°; yield 23% of theoretical value.

EXAMPLE 43

a) 10 g of 5 - methyl - 3 - benzofuran - acetic acid are boiled under reflux for 5 hours with 25 ml of methanol and 0.7 ml of concentrated sulphuric acid. The methanol is then distilled off *in vacuo* and at 30°, the residue taken up with ether and water and the ether phase washed neutral with sodium bicarbonate solution. The ether phase produces, after drying over sodium sulphate and evaporation, 10.4 g of crude 5 - methyl - 3 - benzofuran - acetic acid methyl ester as a yellow oil, which is purified by distillation at 11 Torr. 9.4 g are obtained, B.P. 150°/11 Torr. Yield 87.5% of theory.

b) 9.0 g of the preceding ester and 8.6 g of *p*-ethoxybenzoyl chloride are dissolved in 50 ml of carbon disulphide and to this solution is added, dropwise with stirring within 1 hour, 12.2 g of tin tetrachloride. The mixture is then stirred for 20 hours at room temperature. The reaction mixture is then rimed into a separating funnel with chloroform and decomposed by shaking with water. The organic phase is washed neutral with water, dried over sodium sulphate and evaporated *in vacuo*. The residual oil gives, from methanol, 10 g of crystalline 2 - (p - ethoxybenzoyl) - 5 - methyl - 3 - benzofuranacetic acid methyl ester, M.P. 132—133°. Yield 65% of Theory.

c) 0.55 g of the preceding ester are boiled under reflux for 16 hours with 10 ml of piperidine, the excess piperidine is then distilled off *in vacuo* and the residual oil crystallised from ether/petrol ether. 0.27 g of 2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuran-acetic acid piperidide are obtained, M.P. 100—102°. Yield 43% of Theory.

d) 0.18 g of the preceding piperidide are mixed with 5 ml of 1.8 molar diborane solution in tetrahydrofuran and the mixture kept at room temperature for 16 hours. The reaction mixture is then evaporated *in vacuo*, the residue mixed with 5 ml of methanol and to the resulting solution is added 1 ml of a solution of hydrogen chloride in ether. The reaction mixture is then boiled for 1 hour under reflux. It is then evaporated *in vacuo*, the residue taken up with water and extracted with ether. The ether phase is removed and the aqueous solution freed from neutral material is made alkaline with 2-N sodium hydroxide solution and the liberated base extracted with ether. The ether extract is washed neutral, dried over sodium sulphate and evaporated. The residual oil is dissolved in acetone and ether and a small excess of a solution of hydrogen chloride in ether is added. By scratching 0.12 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrochloride are obtained, M.P. 192—193°. Yield 58% of theory.

e) Analogously to c) 0.5 g of 2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuran - acetic acid methyl ester are treated with 10 ml of pyrrolidine. 0.3 g of 2 - (*p* - ethoxybenzoyl) - 5 - methyl - 3 - benzofuran - acetic acid pyrrolidide are obtained as an oil, which is reduced analogously to d), without further purification, with 5 ml of diborane solution. Crystallisation from acetone produces 0.15 g of 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine - hydrochloride, M.P. 167—169°. Yield 49% of theory.

f) Analogously to b) is obtained from 9.0 g of 5 - methyl - 3 - benzofuran - acetic acid methyl ester and 9.3 g of *p* - isopropoxy - benzoyl chloride after treatment with 12.8 g

of tin tetrachloride, final processing and crystallisation from methanol 10.0 g of 2 - (*p* - isopropoxy benzoyl) - 5 - methyl - 3 - benzofuran - acetic acid methyl ester, M.P. 97—99°. Yield 62% of theory.

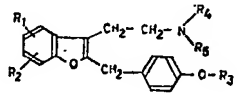
g) Analogously to c) is obtained from 0.5 g each time of the preceding ester the pyrrolidide yield 61% of theory and the piperidide, yield 55% of theory. These amides produce after reduction analogously to d), the 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride from acetone/ether, M.P. 191—192°, (Yield 51% of Theory), and the 1 - [2 - [2 - (*p* - isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine hydrogen sulphate from acetone, M.P. 171—172°. Yield 53% of theory.

h) Analogously to a) is obtained from 11 g of 5 - chloro - 3 - benzofuran - acetic acid 10 g of 5 - chloro - 3 - benzofuran - acetic acid methyl ester as oil. Yield 87% of theory.

i) Analogously to b) 10 g of the preceding ester are acylated with 9.6 g of *p* - ethoxy - benzoyl chloride and 13.6 g of tin tetrachloride as catalyst. 5.0 g of 2 - (*p* - ethoxybenzoyl) - 5 - chloro - 3 - benzofuran - acetic acid methyl ester are obtained as an oil. Yield 33% of theory. Analogously to c) 0.5 g of this oil are converted to the pyrrolidide, yield 50% of theory, and this, analogously to d), is reduced with 5 ml of diborane solution. Crystallisation from acetone/water gives the 1 - [2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine hydrochloride, M.P. 196—197°. Yield 57% of theory.

WHAT WE CLAIM IS:—

1. Benzofuran derivatives having the general formula I



(I)

wherein

R_1 represents a hydrogen atom, a halogen atom up to and including the atomic number 35 or a methyl, ethyl, methoxy, ethoxy or nitro group,

R_2 represents a hydrogen atom, a halogen atom up to and including the atomic number 35 or a methyl, ethyl, methoxy or ethoxy group,

R_3 represents an alkyl group having at most 4 carbon atoms, and

R_4 and R_5 individually represent alkyl groups having at most 4 carbon atoms, or together with the adjacent nitrogen atom they represent a pyrrolidino, piperidino or morpholino group,

as well as their pharmaceutically acceptable acid addition salts.

2. 1 - [2 - [2 - (*p* - Ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine.

3. 1 - [2 - [2 - (*p* - Ethoxybenzyl) - 5,6 - dimethyl - 3 - benzofuranyl] - ethyl] - pyrrolidine.

4. N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 6 - methyl - 3 - benzofuran] - ethylamine.

5. 1 - [2 - [2 - (*p* - Ethoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine.

6. 4 - [2 - [2 - (*p* - Isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - morpholine.

7. 1 - [2 - [2 - (*p* - Ethoxybenzyl) - 5 - chloro - 3 - benzofuranyl] - ethyl] - pyrrolidine.

8. N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - methoxy - 3 - benzofuran] - ethylamine.

9. N,N - di - n - propyl - 2 - [2 - (p - ethoxybenzyl) - 5 - methyl - 3 - benzofuran] - ethylamine.

10. 1 - [2 - [2 - (*p* - Isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - piperidine.

11. 1 - [2 - [2 - (*p* - Isopropoxybenzyl) - 5 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine.

12. 1 - [2 - [2 - (*p* - Ethoxybenzyl) - 6 - methyl - 3 - benzofuranyl] - ethyl] - pyrrolidine.

13. 1 - [2 - [2 - (*p* - Ethoxybenzyl) - 6 - ethyl - 3 - benzofuranyl] - ethyl] - pyrrolidine.

14. N,N - diethyl - 2 - [2 - (*p* - ethoxybenzyl) - 5 - chloro - 3 - benzofuran] - ethylamine.

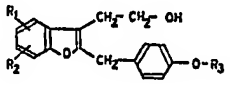
15. 1 - [2 - [2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl] - ethyl] - piperidine.

16. 4 - [2 - [2 - (*p* - ethoxybenzyl) - 3 - benzofuranyl] - ethyl] - morpholine.

17. The pharmaceutically acceptable acid addition salts of a compound as claimed in any one of claims 2 to 16.

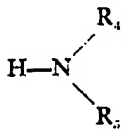
18. The hydrochloride of a compound as claimed in any one of claim 2 to 16.

19. Proess for the production of benzofuran derivatives having the general formula I as defined in claim 1, or their pharmaceutically acceptable acid addition salts, which comprises reacting a reactive ester of the corresponding compound having the general formula II



(II)

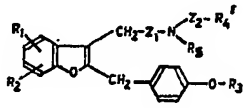
with an amine having the general formula III



(III)

wherein R_4 and R_5 have the meanings given in claim 1, and, when required, converting a benzofuran derivative having the general formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

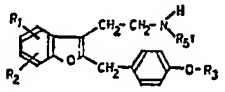
20. Process for the production of benzofuran derivatives having the general formula I as defined in claim 1, or their pharmaceutically acceptable acid addition salts, which comprises reducing, by means of a complex hydride, the corresponding compound having the general formula VIII



(VIII)

wherein one of the symbols Z_1 and Z_2 represents a methylene group and the other a carbonyl group,
R_1, R_2 and R_3 have the meanings given in claim, 1 and
R_4' represents an alkyl group having at most 3 carbon atoms or together with R_5, Z_2 and the adjacent nitrogen atom, depending on the meaning of Z_2, an optionally carbonyl-substituted pyrrolidino, piperidino or morpholino group,
directly, or after reaction with triethyloxonium fluoroborate, to give the corresponding immonioethyl ester fluoroborate, and, when required, converting a benzofuran derivative having the general formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

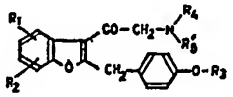
21. Process for the production of benzofuran derivatives having the general formula I as defined in Claim 1 or their pharmaceutically acceptable acid addition salts, which comprises reacting the corresponding compound having the general formula IX



(IX)

wherein
R_5' represents a hydrogen atom or an alkyl group having at most 4 carbon atoms,
with a lower oxoalkane containing maximally 4 carbon atoms under reducing conditions, or with a reactive ester of a lower alkanol containing maximally 4 carbon atoms in the presence of an acid-binding agent, using, in each case, at least the molar equivalent of the said oxoalkane or reactive ester corresponding to the number of hydrogen atoms bound to the nitrogen atom to be replaced or, if R_5' is hydrogen, also with a reactive ester of 1,4-butane-diol, 1,5-pentanediol or diethylene glycol in the presence of an acid-binding agent and, when required, converting a benzofuran derivative having the general formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

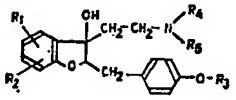
22. Process for the production of benzofuran derivatives having the general formula I as defined in claim 1 or their pharmaceutically acceptable acid addition salts, which comprises reducing the corresponding compound having the general formula X



(X)

wherein R_1 to R_5 have the meanings given in claim 1, by means of a complex hydride, in the presence of a Lewis acid and in an ethereal solvent and, when required, converting a benzofuran derivative, having the general formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

23. Process for the production of benzofuran derivatives having the general formula I as defined in claim 1 or their pharmaceutically acceptable acid addition salts, which comprises subjecting the corresponding compound having the general formula XI

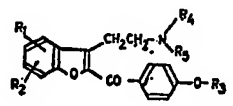


(XI)

wherein R_1 to R_5 have the meaning given in claim 1, to conditions under which water is split off and, when required, converting a benzofuran derivative having the general formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

24. Process for the production of benzofuran derivatives having the general formula I as defined in claim 1 or their pharmaceutically acceptable acid addition salts, which

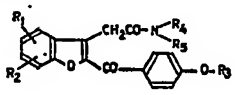
comprises reducing the corresponding compound having the general formula XII



(XII)

wherein R_1 to R_5 have the meanings given in claim 1, by means of a complex hydride, or hydrazine hydrate in the presence of an alkali metal hydroxide and, when required, converting a benzofuran derivative having the general formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

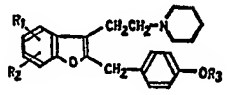
25. Process for the production of benzofuran derivatives having the general formula I as defined in claim 1 or their pharmaceutically acceptable acid addition salts, which comprises reducing the corresponding compound having the general formula XIII



(XIII)

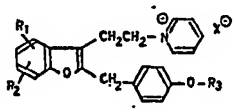
wherein R_1 to R_5 have the meanings given in claim 1, by means of a complex hydride and, when required, converting a benzofuran derivative having the general formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

26. Process for the production of benzofuran derivatives having the general formula Ia,



(Ia)

wherein R_1, R_2 and R_3 have the meanings given in claim 1, except that R_1 may not represent a nitro group, or their pharmaceutically acceptable acid addition salts, which comprises reducing the corresponding compound having the general formula XIV



(XIV)

wherein R_1 to R_3 have the meanings given in claim 1 except that R_1 may not represent a nitro group, and $X^{\ominus}$ represents a monovalent anion or the normal equivalent of a polyvalent anion, by means of catalytically activated hydrogen and, when required, converting a benzofuran derivative having the general formula Ia thus obtained into a pharmaceutically acceptable acid addition salt thereof.

27. Benzofuran derivatives having the general formula I as defined in claim 1, or pharmaceutically acceptable acid addition salts thereof, whenever prepared by a process as claimed in any one of claims 19 to 23.

28. Benzofuran derivatives having the general formula I as defined in claim 1, or pharmaceutically acceptable acid addition salts thereof, whenever prepared by a process as claimed in any one of claims 24 to 26.

29. Process for the production of benzofuran derivatives having the general formula I as defined in claim 1 as well as their pharmaceutically acceptable acid addition salts substantially as hereinbefore described with reference to any one of Examples 1 (excluding part c'), 2(a), 3, 4, 5(a), 6(a)—(e), 7, 8(a), 9, 11 to 16, 17(a)—(h), 18(i), 19(a)—(e), 20(a)—(b), and 22(i).

30. Process for the production of benzofuran derivatives having the general formula I as defined in claim 1 as well as their pharmaceutically acceptable acid addition salts substantially as hereinbefore described with reference to any one of the Examples 1 (including part c'), 2(b)—(c), 5(b), 6(f), 8(b), 10, 18(ii), 19(f)—(g), 20(c), 22(ii) and 23 to 43.

31. Benzofuran derivatives having the general formula I as defined in claim 1, or pharmaceutically acceptable acid addition salts thereof, whenever prepared by a process as claimed in claim 29.

32. Benzofuran derivatives having the general formula I as defined in claim 1, or pharmaceutically acceptable acid addition salts thereof, whenever prepared by a process as claimed in claim 30.

33. A pharmaceutical composition comprising a benzofuran derivative having the general formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier therefor.

34. A pharmaceutical composition as claimed in claim 33 substantially as hereinbefore described with reference to any of the foregoing prescriptions.

W. P. THOMPSON & CO.,
Chartered Patent Agents,
Cooper's Buildings, Church Street,
Liverpool, L1 3AB.

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